The Syntheses of β-Lactam Antibiotics from 3-Formylcephalosporins as the Key-intermediates

Een wetenschappelijke proeve op het gebied van de Natuurwetenschappen, Wiskunde en Informatica

Proefschrift

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door

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"*Experiment is the sole interpreter of the artifices of Nature*"
Leonardo da Vinci (1452-1519)

Aan mijn ouders

Paranimfen
René Gieling
Sander Hornes

VOORWOORD

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Rolf

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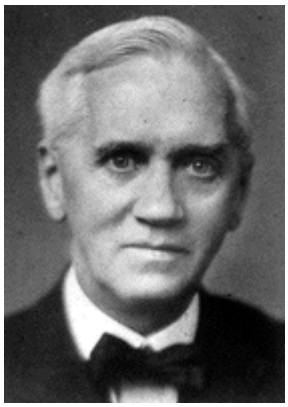
1 INTRODUCTION

1.1 Background

History

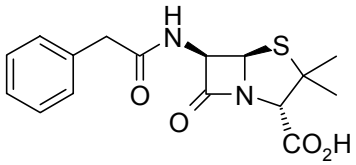
Even half a century after their introduction β-lactam drugs are still the most widely prescribed antibiotics in medicine. Although anti-bacterial effects of molds had been reported and even investigated at least several times, the history of this class of drugs really began with their serendipitous discovery by Alexander Fleming (1881-1955) in 1928 (Figure 1).[1],[2] Returning to his laboratory at St. Mary's Hospital in London after a short vacation, he observed a blue mold growing in a Petri-dish which originally had been overgrown with colonies of staphylococci. Around the mold there was a halo within which no bacterial colonies were growing. The mold evidently had produced a lethal substance, which diffused outward through the culture media, thereby killing bacteria wherever they were present. Fleming learned that the medium containing the anti-bacterial substance, which he named *penicillin* after the mold *Penicillium notatum*, was not toxic to laboratory animals.[1],[3]



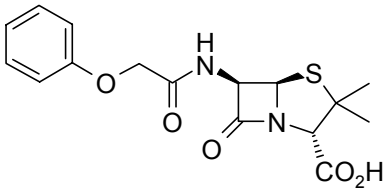
Alexander Fleming (1881-1955).

Figure 1.

The priority of other duties at the hospital prevented further scrutiny of his observations. Moreover, the advent of sulfa drugs led to a general disinterest in Fleming's first disclosure. It was not until 1938 that penicillin came under renewed investigation by Walter Florey and Ernst Boris Chain at Oxford University.[4] They confirmed Fleming's results and succeeded in the isolation of an impure material with unique potent killing power towards certain germs in test animals. In 1942, Chain produced penicillin G (**1**), a yellow powder, which was successfully used by Fleming against meningitis (Figure 2). By that time, Florey had visited the United States where plans were set up for the industrial production of penicillin by Merck, Pfizer, and Squibb, supported by the federal government.[5] This heavily subsidized research and production in a relatively short time, led to the large-scale manufacture of penicillin. Sufficient large quantities of penicillin became available for administering to wounded soldiers on the battlefields. In 1943, a British radio broadcast on the invention of a remarkable medicine aroused the attention of researchers at Gist-brocades (at that time named "Nederlandsche Gist- en Spiritusfabriek"). This news, in combination with information from scarcely available literature was the start of a research program which led to the development of several penicillin-derived drugs and intermediates.[6] After World War II, it became clear that an astonishing 95% of soldiers with infection injuries had survived thanks to medication with penicillin. In 1945, Fleming, Chain, and Florey were jointly awarded the Nobel Prize in physiology and medicine for their discovery of penicillin G.



1 penicillin G



2 penicillin V

Figure 2.

In this early period of penicillin, considerable effort was devoted to fundamental aspects of the chemistry of penicillin G. Studies in Britain and the United States soon revealed the existence of more compounds with penicillin activity. In 1949, when the structure of penicillin G (**1**) was finally elucidated by Dorothy Crowfoot-Hodgkin,[7] it was found that these compounds had the same general structure as penicillin but with different side chains. It soon became apparent that these penicillins could not be easily synthesized on a large scale. However, the use of various biosynthetic procedures in a well-considered way gave access to a large variety of penicillins. In 1957, after nine years of scrutinizing work, John C. Sheehan and K.R. Henry-Logan completed the total synthesis of penicillin V (**2**) (Figure 2).[8] The isolation of 6-amino-penicillanic acid, the *β*-lactam nucleus of both penicillin V and G, by scientists from Beecham in 1957, was a major contribution to the development and production of semi-synthetic penicillins.[9]

Another important milestone in the search for new *β*-lactam antibiotics has been the discovery by Abraham and Newton[10] at Oxford in 1953 that a fungus of the genus *Cephalosporium* produces a number of potent antibiotics, among which cephalosporin C (**3**) (Table 1). Great interest arose when it appeared that this antibiotic showed broad-spectrum activity. It was active against both Gram-positive and Gram-negative bacteria, it was inert towards hydrolysis by certain penicillinases, and it had a similar low toxicity as the penicillins.[11] The discovery of the cephalosporins opened a new field of research aimed at the search for and exploration of more active and different anti-bacterial compounds. As the penicillins and cephalosporins are chemically sensitive compounds, chemical progress in this field of antibiotics has depended heavily on the use of modern analytical and purification techniques and on the development of more selective reagents and protecting groups. A considerable boost to the chemical morale of synthetic chemists working in this field was given by Woodward's total synthesis of cephalosporin C (**3**).[12]

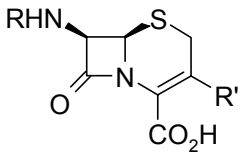
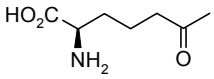
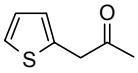
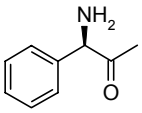
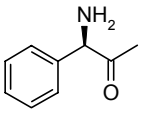


Table 1. *Important early cephalosporins.*

R:	R':	name:	nr.:	year of discovery:
	CH_2OAc	cephalosporin C	**3**	(1953)
	CH_2OAc	cephalotin	**4**	(1962)
	CH_3	cephalexin	**5**	(1967)
	Cl	cefaclor	**6**	(1974)

Modern large-scale fermentation methods have enabled penicillin production to reach a level of more than four thousand tons annually. As a consequence, penicillins can now be regarded as a commercially available synthetic bulk intermediate for other, more sophisticated β-lactam antibiotics. Since the cephalosporins are generally more expensive to produce than the penicillins, numerous chemical studies have been performed to achieve economical conversion of penicillins into the cephalosporins. Such transformation requires an oxidation of one of the methyl groups of penicillin and a ring expansion of the thiazolidine moiety. These stringent requirements were eventually fulfilled in a novel process originally described by Morin *et al*..[13] After this breakthrough, the chemistry of cephalosporins developed rapidly and very soon a large variety of cephalosporins became available on an industrial scale.

In 1962, combined synthetic efforts led to the first semi-synthetic cephalosporin cephalotin (**4**), which was remarkably active against penicillin-resistant *Staphylococcus*. Further developments within the cephalosporin family resulted in orally active formulations, *e.g*. cephalexin (**5**) and cefaclor (**6**) (Table 1). The synthesis of the latter compound is a brilliant tour de force in synthetic organic chemistry.

Mode of action and mechanism of resistance of penicillin-type antibiotics

The cell-wall of bacteria partly consists of peptidoglycan, which is essential for the stability of the cell-wall. The final step in the cell-wall synthesis in bacteria is the formation of peptide cross-links between adjacent glycan chains (formation of peptidoglycan). The formation of the peptide cross-links involves an unusual type of peptide formation, called transpeptidation. This transpeptidation is inhibited by β-lactam antibiotics, and thus an imperfect, weakened peptidoglycan is formed leading to death of the growing bacteria (Figure 3). When the formation of the cell-wall, catalyzed by autolysins, continues, further weakening of the cell wall damage leads to osmotic lysis, followed by death.[14]

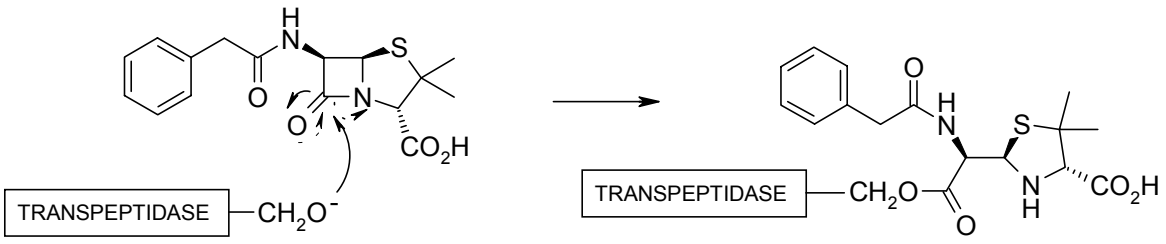


Figure 3. *Transpeptidase inhibition by a penicillin molecule..*

In spite of the therapeutic success of the early β-lactam antibiotics, the anti-bacterial activity of the first-generation drugs against certain Gram-negative "problem germs" was not sufficient. Already a few years after the second world war, strains of *Staphylococcus aurus* had emerged that were immune to penicillin.[15] Since then, bacterial resistance towards antibiotics has spread and has become a serious threat to humanity. Bacteria have developed several creative mechanisms for protection against antibiotics and are even capable of passing the genes responsible for the resistance to other bacteria.[15] A defense mechanism active against β-lactam antibiotics utilizes β-lactamases, which are enzymes that hydrolyze the β-lactam ring of the antibiotic.[16] As the β-lactam ring is the bioactiphore of both penicillins and cephalosporins, these antibiotics become inactive.

The methicillin-resistant *Staphylococcus aurus* (MRSA) is a notorious example of a highly dangerous bacteria strain.[17] This strain is resistant to all β-lactam antibiotics due to the presence of an additional penicillin-binding protein (PBP2a) for which β-lactams have a high affinity.[18] Vancomycin[19] and Synercid[20] are the only marketed drugs that are effective against MRSA infections. In addition to the complications caused by the restricted options for treatment, vancomycin-resistant

MRSA[21] has recently been detected in hospitals in Japan[22] and the USA.[23] Furthermore, the hospital setting is no longer the exclusive domain of MRSA infections. Recently, there have been alarming reports of its spread in nursing homes, extended-care facilities, and a day care center.[24] The problem of resistance is dramatically enhanced by inappropriate and uncritical prescription by medical doctors, incorrect usage of the antibiotics by patients, and the excessive use of penicillins in animal feeding.

Possible solutions for the resistance problem

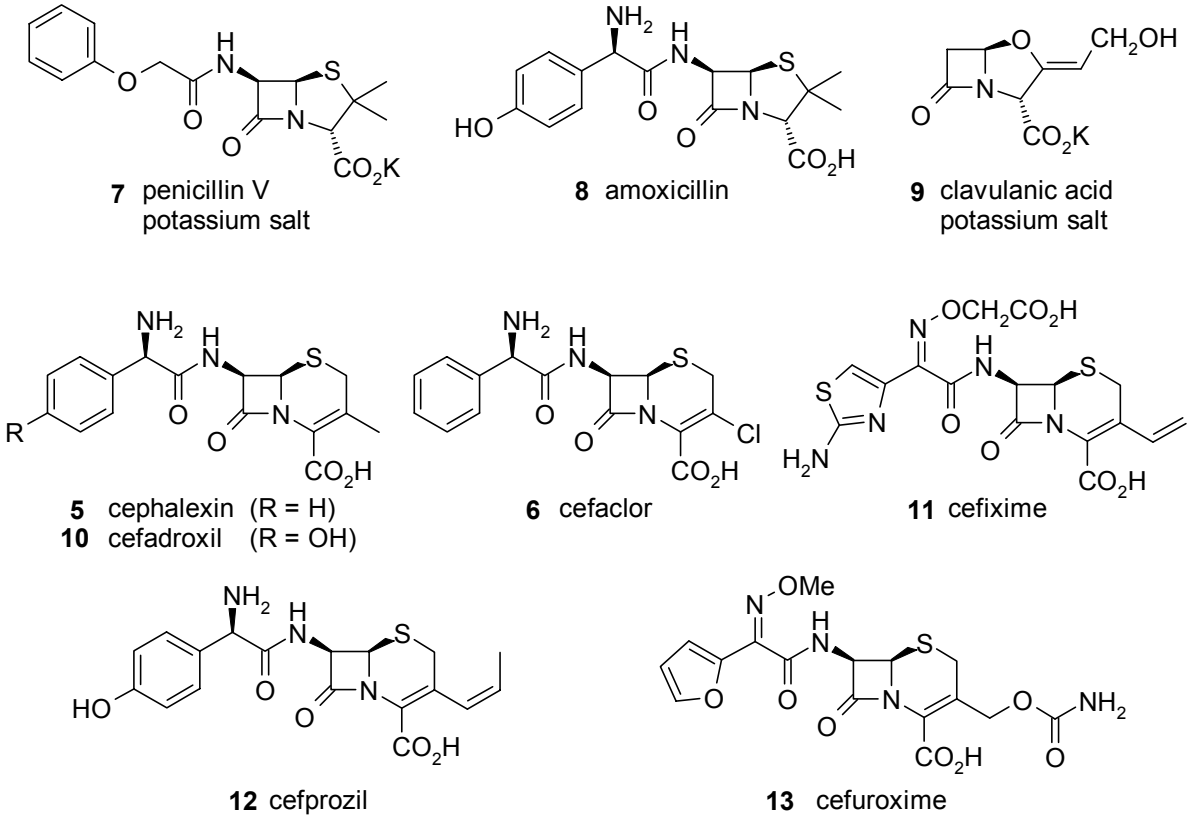
A provisional solution for the β-lactamase problem is using a combination of the antibiotic and the potassium salt of clavulanic acid (**9**) (Figure 4). Although clavulanic acid is not very effective as an antibiotic, it inhibits the activity of β-lactamases. In combination with β-lactamase-sensitive penicillins and cephalosporins, clavulanic acid therefore causes a distinct increase in the activity of these antibiotics. It can be expected, however, that bacteria also will adapt rapidly to this combination drug as well.

Another conceivable solution to the problem of persistent resistance can be the responsible prescription for the use of antibiotics. Bacterial which have developed a resistance towards certain antibiotics, also have acquired a more complex metabolism. Due to the extra genetic luggage inherent to the additional metabolism, resistant bacteria will loose their resistance to an antibiotic when they are no longer exposed to it. This process is essentially the same as the evolutionary process that made them resistant. Therefore, the abovementioned tools are important to solve the resistance problem to an extent that many antibiotics will continue to serve as life-saving drugs during the 21st century.

Many companies are looking for novel classes of anti-bacterial agents. An effective strategy to discover compounds with activity against resistant organisms involves synthetic modulation of a known class of anti-bacterial agents with pronounced activity.[25] Since cephalosporins have an excellent safety profile and are synthetically accessible from commercial sources, the development of new derivatives of these compounds is a very promising avenue for the identification of anti-MRSA agents. Recent numbers on drug prescription in US show that β-lactam antibiotics are still widely used in medicine. Therefore, the search for new cephalosporin antibiotics remains a profitable issue for the pharmaceutical industry (Figure 4). The

combination of combinatorial chemistry, chemistry on the solid support, and high throughput screening catalyzes this search for new pharmaceuticals.[26]

Figure 4: *β-Lactam antibiotics in the top 200 prescriptions in the US.*[27]



As is evident from the top 200 prescriptions in the United States (Figure 4), the first generation antibiotics (*e.g.* penicillin V (**7**), amoxicillin (**8**), cephalexin (**5**)) as well as the second and third generation cephalosporins (*e.g.* cefaclor (**6**), cefixime (**11**), cefprozil (**8**)) are still very important antibacterial pharmaceuticals.

Since an ideal antibiotic will probably never be found, the war against infectious diseases goes on, in which new chemical entities will be thrown into the fray. New anti-bacterial agents need to be cheap, effective, and non-toxic. Although in recent years the worldwide incidence of antibiotic resistance among Gram-positive bacteria, *e.g. Staphylococcus*, *Streptococcus* and *Enterococcus* species, has increased, major interest is still focused on the development of novel cephalosporin antibiotics in order to improve anti-bacterial activity against resistant bacterial strains.[28] In this respect, it should be emphasized that also the development of new synthetic methodologies and new reactions in the field of penicillin and cephalosporin chemistry is of extreme importance, to enable the synthesis of new entities in this field.

1.2 Aim of the research and outline of the thesis

In 1994, DSM Research and Gist-brocades started the joint-venture Chemferm, which in 1996 initiated the so-called Cluster Project "Fine-Chemistry", a cooperation between four universities and Chemferm. One of the main objectives of this project was to develop improved, or alternative clean, (bio)catalytic, efficient routes for cephalosporin β-lactam antibiotics.

The research described in this thesis is focused on the chemical modification of β-lactam nuclei. In the first phase of the project, most attention was paid to the search for new (green) syntheses or shortcuts for 7-ACCA, the β-lactam core of cefaclor (**6**) (Figure 4), from readily available fermentation products. As a consequence of new insights and developments, as well as of different views of industrial importance, the aims were adjusted to a focus on the chemistry of 3-formylcephalosporins as a versatile class of β-lactam nuclei.

Nature itself is capable of synthesizing 3-formylcephalosporins as part of the metabolism of *Cephalosporium acremonium* (see Chapter 2, Section 2.2). In principle, by blocking or changing the sequel steps by molecular pathway engineering, isolation of 3-formylcephalosporins in large quantities can be envisaged. By means of this environmentally benign bio-approach, a green process for the production of 3-formylcephalosporins might be an opportunity in the future. In view of these "green" prospects of 3-formylcephalosporins, its chemistry fits well in the objectives of the cluster project (*vide supra*). Until now, the 3-formylcephalosporins are only accessible using complicated, multi-step procedures (Chapter 2). The above-sketched green future prospects are a clear stimulus for the development of new chemistry on the basis of 3-formylcephalosporins as the key-intermediates, as is described in this thesis.

Three main objectives can be recognized for this part of the project.

- Finding short, high yielding synthetic routes towards the key-intermediates, 3-formylcephalosporins, from readily available and cheap β-lactam nuclei.
- Exploring the chemistry of 3-formylcephalosporins in order to find alternative, more economical synthetic routes to antibiotics, which have already been commercialized. Special attention is paid to the use of Barton's radical decarboxylation methodology in the cephalosporin system.

- Using the acquired knowledge of cephalosporins for the synthesis of new and interesting *β*-lactam antibiotics.

In Chapter 2, an overview of the syntheses of 3-formylcephalosporins and their use as advanced intermediates in the syntheses of building blocks for *β*-lactam antibiotics will be given. In Chapter 3, a new synthetic methodology is described for the preparation of 3-formylcephalosporins from starting materials readily available by fermentation, *viz.* 7-aminodesacetylcephalosporanic acid (7-ADCA), 7-aminocephalosporanic acid (7-ACA), and cephalolactone. In Chapter 4, a synthetic study concerning the preparation of 3-norcephalosporins from 3-carboxycephalosporins, employing Barton's radical decarboxylation reaction, is presented. The application of a halo-decarboxylation reaction at C_4, using the model substrates 7-phenylacetyl-ADCA and 7-phenylacetyl-ACA, is discussed in detail. In Chapter 5, 3-formylcephalosporins are converted into the corresponding 3-carboxycephalosporins *via* a new procedure. These 3-carboxycephalosporins are then subjected to Barton's radical decarboxylation reaction to produce the corresponding 3-norcephalosporins, applying the optimum conditions established with the model compounds as described in Chapter 4. The results of the radical decarboxylation reactions for both the model compounds (carboxylate at C_4) and the C_3-carboxylates are evaluated in terms of structural differences. One of the objectives was the synthesis of 7-ACCA, the nucleus of cefaclor. This compound could indeed be synthesized from 3-carboxycephalosporins employing Barton's radical decarboxylation procedure. In Chapter 6, the behavior of 3-formylcephalosporins in Wittig-type olefinations is investigated. Chapter 7 is devoted to the diastereoselective Barbier-type organozinc additions to 3-formylcephalosporins, yielding new advanced and promising intermediates for the synthesis of novel *β*-lactam antibiotics.

Summaries in English and Dutch conclude this thesis.

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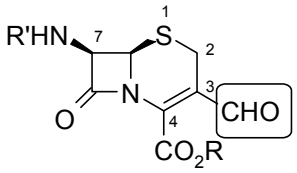
2 SYNTHESIS AND APPLICATIONS OF 3-FORMYLCEPHALOSPORINS: AN OVERVIEW OF THE RELEVANT LITERATURE

2.1 Introduction

This chapter contains a literature overview relevant for the research described in the following chapters. The formyl group at the 3-position of the cephalosporin nucleus is highly instrumental in the synthesis of a large variety of cephalosporins with structural modifications at C_3 (Figure 1). In this review, various aspects of the chemistry of these key-intermediates are covered. First, all reported syntheses of 3-formylcephalosporins are described. The second part deals with applications and reactions of 3-formylcephalosporins. Especially the chemistry of the 3-formylgroup is discussed. In general, protection-deprotection steps are only mentioned when important.

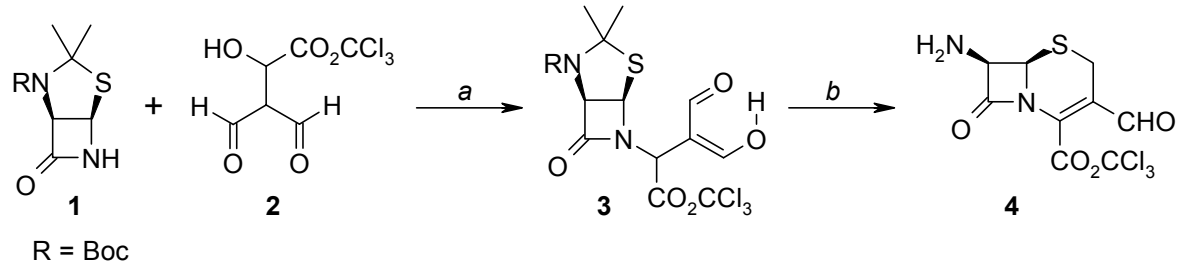


3-formylcephalosporins

Figure 1.

2.2 Synthesis of 3-formylcephalosporins

In the late 60s the first synthesis of a 3-formylcephalosporin has been reported.[1],[2] In the famous total synthesis of cephalosporin C by Woodward *et al.*[1] 3-formylcephalosporin **4** constitutes an important intermediate. In this synthesis, *β*-lactam **1** was condensed with dialdehyde **2** to afford adduct **3**, which, on treatment with trifluoroacetic acid was transformed to aminoaldehyde **4** (Scheme 1).

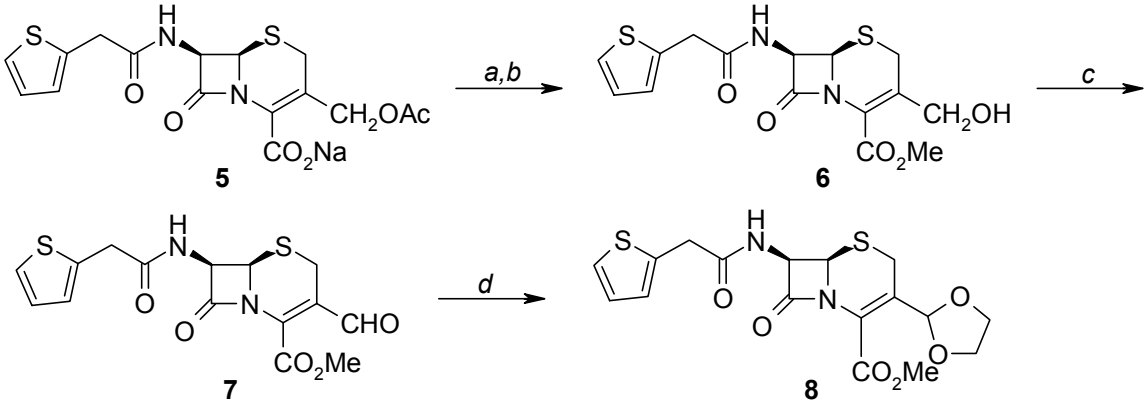


a) n-octane, 80°C; b) TFA.

Scheme 1.

The authors wrote: "this sensitive intermediate (aldehyde **4**) was used in subsequent reactions without extensive purification". This was the start of numerous studies aimed to use these sensitive 3-formylcephalosporins for the syntheses of novel types of *β*-lactam antibiotics with other or better anti-bacterial properties.

Most reported syntheses involve, at the same stage, deacetylation of the acetoxy group at C_3 (*e.g.* of **5**) using *citrus acetylesterase* (Scheme 2).[3] Cautious acidification, followed by extraction into an organic solvent and subsequent treatment with diazomethane, leads to methyl ester **6**, which was contaminated with some lactone, in 65-75% yield.[2]

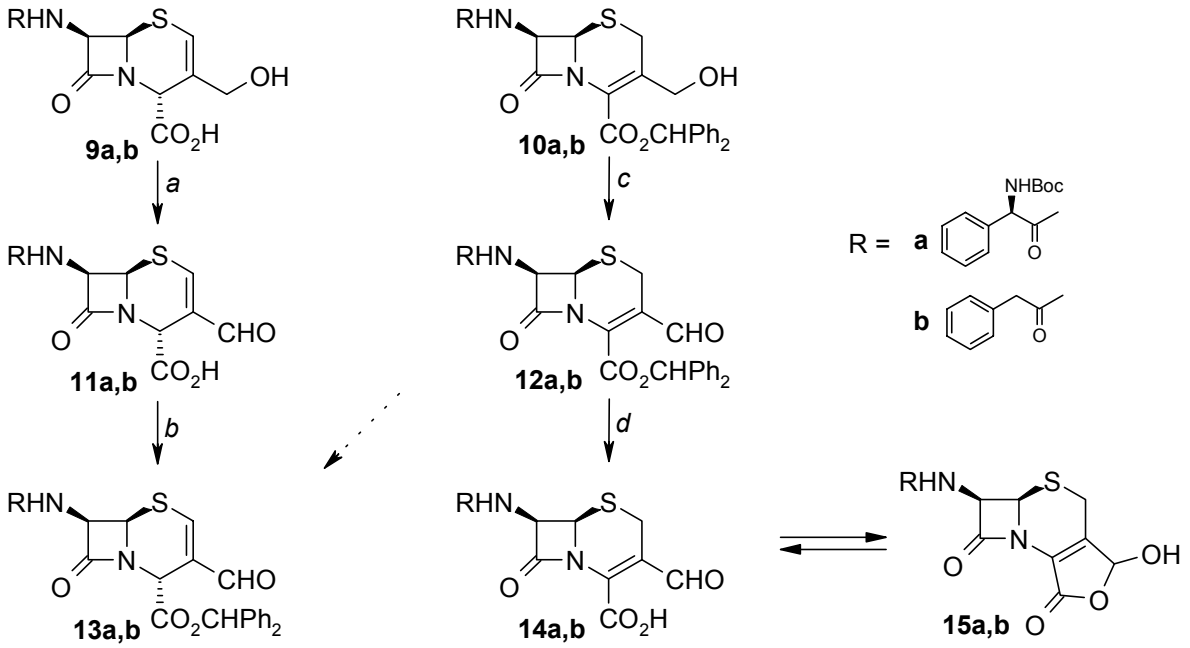


a) citrus acetylesterase; b) CH_2N_2; c) MnO_2; d) ethylene glycol, acid.

Scheme 2.

Oxidation of the hydroxymethyl group with manganese(IV) oxide gave aldehyde **7** in only 17% yield, which was converted directly into the ethylene acetal **8**. Attempts to hydrolyze aldehyde **7** to the free acid were unsuccessful. The corresponding thioketal was synthesized from **7** by reaction with dimercapto ethane in 86% yield.[4]

An alternative synthesis of 3-formylcephalosporins by Peter *et al*.[5] is outlined in Scheme 3. The synthesis starts from the 3-substituted hydroxymethyl compounds **9** or **10**, which can be obtained by a route similar to that depicted in Scheme 2. Attempts to oxidize the hydroxyl group in **10** with chromium(VI) oxide and acetic acid or manganese(IV) oxide in dichloromethane failed, because the diphenylmethyl ester was not inert under the reaction conditions. Only the Moffat oxidation (DMSO/acetic anhydride or DMSO/benzoic acid anhydride) successfully led to aldehydes **11** and **12**. The yields ranged from 30 to 90%. Depending on the substrate a small amount of the corresponding Δ^2-isomer **13** may be formed as well.



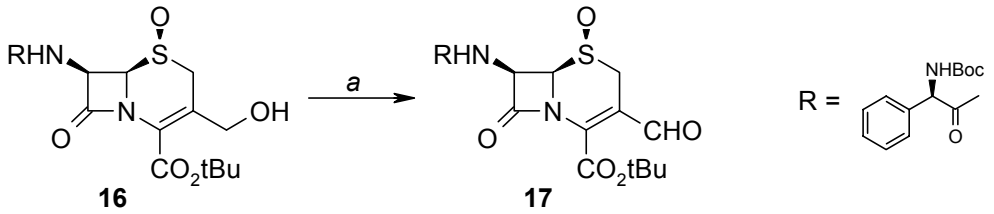
a) DDQ or CrO_3, H_2SO_4; b) Ph_2CN_2; c) DMSO, Ac_2O or DMSO, $(PhCO)_2O$ or CrO_3, pyridine; d) TFA.
Scheme 3.

Later, it turned out that also the Collins method (chromium(VI) oxide/pyridine) leads to the corresponding 3-formylcephems. The formation of hydroxylactones **15** is a competitive reaction in the Δ^3-systems **14**, which are obtainable from **12**. In the Δ^2-series (*viz*. **9** to **13**) such lactonization can not occur. Good yields of **11** were obtained from **9** with dichlorodicyanoquinone (88%) or chromium(VI) oxide/sulfuric acid

(Jones oxidation; 70% yield) as the oxidizing reagents.[1] Esterification with diphenyldiazomethane afforded smoothly the 3-formylceph-2-ems **13** (Scheme 3).

More recently, the abovementioned Δ^3-alcohols **10** were efficiently oxidized with IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) in DMSO to give the corresponding aldehydes **12a** and **12b** in excellent yields of 91% and 94%, respectively.[6]

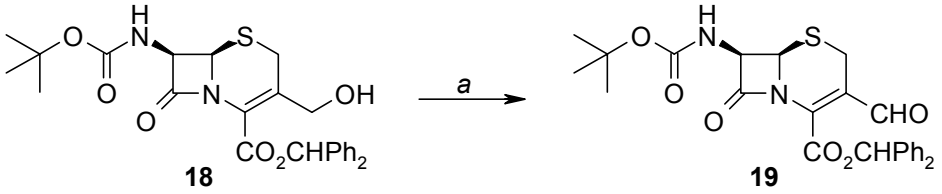
Webber *et al*.[7] also used the Jones oxidation for the transformation of alcohol S-oxide **16** into the corresponding aldehyde **17**, in an excellent yield of 98% (Scheme 4).



a) CrO_3, H_2SO_4.

Scheme 4.

Only one example was reported in which the well-known Swern oxidation is employed for the preparation of a 3-formylcephalosporin. Nagano *et al*.[4] obtained Δ^3-aldehyde **19** from the corresponding alcohol **18** in 73% yield (Scheme 5). This example is rather unique, as no other groups use the Swern oxidation for such transformation in the cephalosporin system.

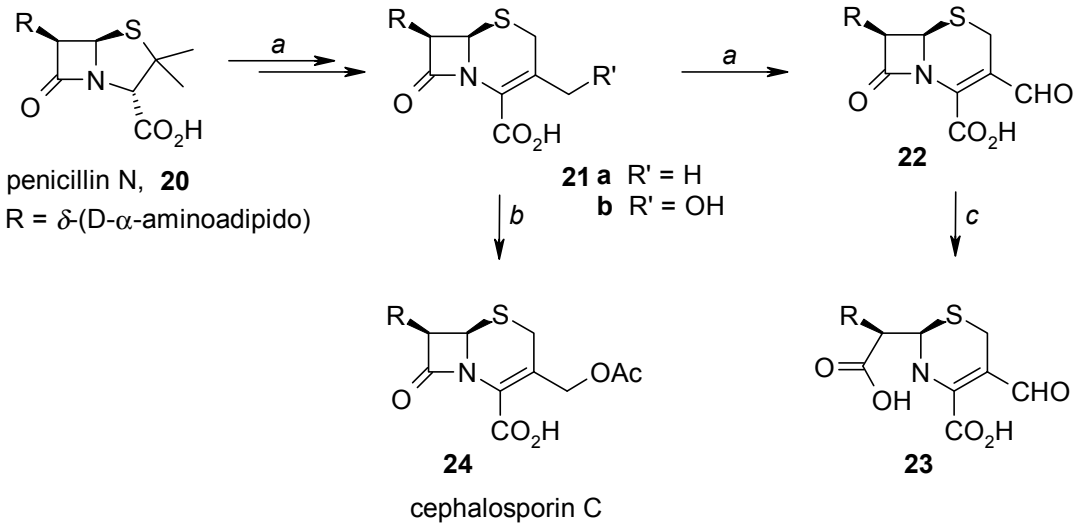


a) oxalyl chloride, Et_3N, DMSO.

Scheme 5.

Nature is also capable of synthesizing a 3-formylcephalosporin.[8] The three final steps in the biosynthesis of cephalosporin C (**24**) in *Cephalosporium acremonium* involve sequentially: (a) the oxidative ring expansion of penicillin N (**20**) to deacetoxycephalosporin C (DAOC; **21a**), (b) the hydroxylation of DAOC **21a** to deacetylcephalosporin C (DAC; **21b**), followed by (c) the acetylation of DAC **21b** to cephalosporin C (**24**) (Scheme 6). Fujisawa and co-workers have reported the generation of mutants, derived of *C. acremonium* ATCC 14553, in which the terminal

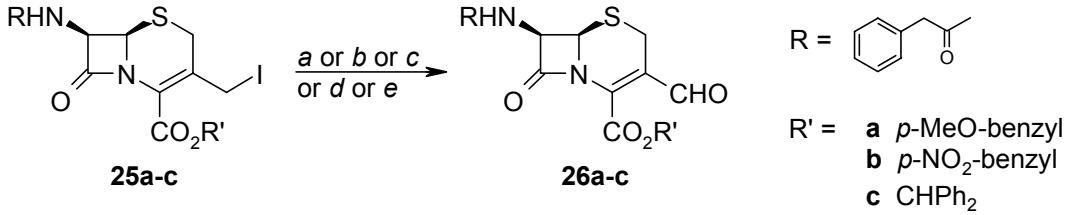
acetyl transfer was blocked. As a result, accumulation of DAC **21b** was observed in the culture broth.[9] Eventually, a new metabolite, *viz*. aldehyde **23**, was isolated from one of the mutants defective in the acetyl transfer step.[10] During the formation of **22**, the enzyme deacetoxycephalosporin C / deacetylcephalosporin C synthase (DAOC/DAC synthase) is apparently capable of oxidizing DAC **21b** to the 3-formylcephalosporin **22**. A spontaneous non-enzymatic hydrolysis of **22** leads then to ring-opened aldehyde **23** (Scheme 6).



a) DAOC/DAC synthase; b) DAC O-acetyltransferase; c) non-enzymatic hydrolysis.

Scheme 6.

3-Formylcephalosporins are also accessible through oxygen or air oxidation of 3-iodomethylceph-3-ems **25a-c** applying rhodium(III) chloride in a catalytic fashion in the presence of aluminum powder in DMF, affording **26a-c** in isolated yields up to 66% (Scheme 7).[11] The reaction can also be carried out in an autoclave under an oxygen atmosphere in DMF.[12]



a) $RhCl_3$, O_2, Al, DMF; b) O_2, DMF; c) $VOSO_4$, $VO(acac)_2$, O_2, Al; d) NaI, MeOH, CH_2Cl_2; e) NMP, O_2, phosphomolybdic acid.

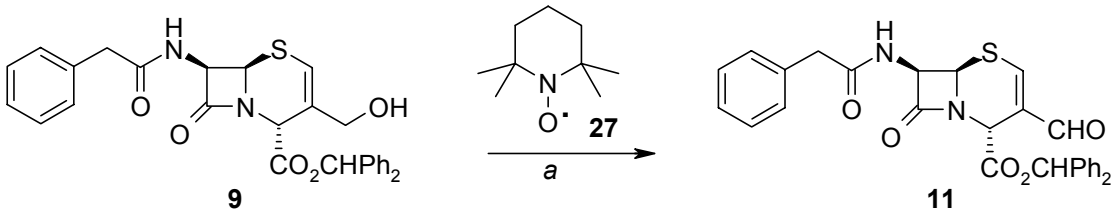
Scheme 7.

When the reaction was performed with at least an equimolar amount of vanadyl sulfate or vanadyl acetonate, similar yields of **26** were obtained from **25**.[11] Without

such a catalyst, but under an oxygen atmosphere in the presence of sodium iodide dissolved in a methanol-dichloromethane solvent mixture, the dimethyl acetal of aldehyde **26a** was formed in 40% yield at the maximum.[13] It is assumed that the reaction proceeds *via* a hypervalent iodine species.

Tanaka *et al*.[14] reported an aerobic oxidation of 3-iodomethylcephalosporin **25a** in N-methyl-pyrrolidone (NMP) in the presence of phosphomolybdic acid (22 wt%). The corresponding 3-formyl compound **26a** was obtained in a moderate yield of 54%.

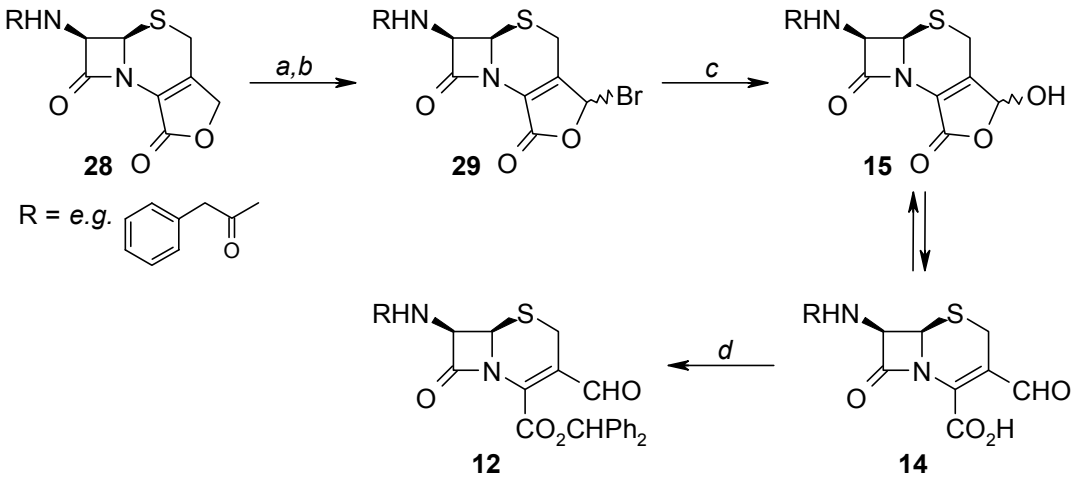
Catalytic oxidation methods are of great interest for industrial applications and accordingly also for the syntheses of 3-formylcephalosporins. Bruno *et al*.[15] claim an effective method (>90% yield) for the oxidation of the hydroxymethyl group in cephalosporins *e.g*. **9** using TEMPO **27** as the catalyst (Scheme 8).



a) NaOCl, CH_2Cl_2, KBr.

Scheme 8.

A completely different approach, starting from the readily available cephalosporin lactones **28**, was used to synthesize 3-formylcephalosporins **12** (Scheme 9).[16]



a) TMSCl, Et_3N, DMF; b) Br_2; c) DMSO; d) Ph_2CN_2.

Scheme 9.

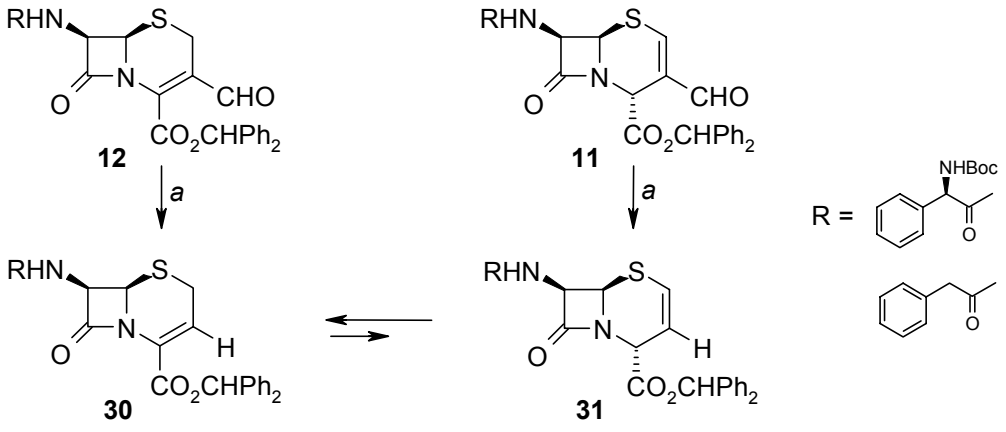
Cephalosporin C_{10}-bromolactones **29** were prepared in good yields (73-78%) *via in situ* silylation of **28** at the C_{10}-position, followed by bromination with molecular bromine. Conversion of **29** into the hydroxylactone **15** was achieved smoothly in quantitative yield by stirring it in a DMSO solution at room temperature. Treatment of the hydroxylactone **15**, which is in equilibrium with its open aldehyde **14**, with diphenyldiazomethane afforded aldehyde **12** in 81-98% yield. The hydroxylactones have also been synthesized directly from 3-hydroxymethyl cephalosporins, which possess a free carboxylate at the C_4 position.[17] In this patent, the hydroxymethyl group is oxidized with a hexavalent chromium compound.

2.3 Reactions with 3-formylcephalosporins

2.4 Removal of the 3-formyl group

Removal of the 3-formyl group in order to synthesize 3-norcephalosporins can be accomplished by direct decarbonylation, or by performing a Baeyer-Villiger oxidation.

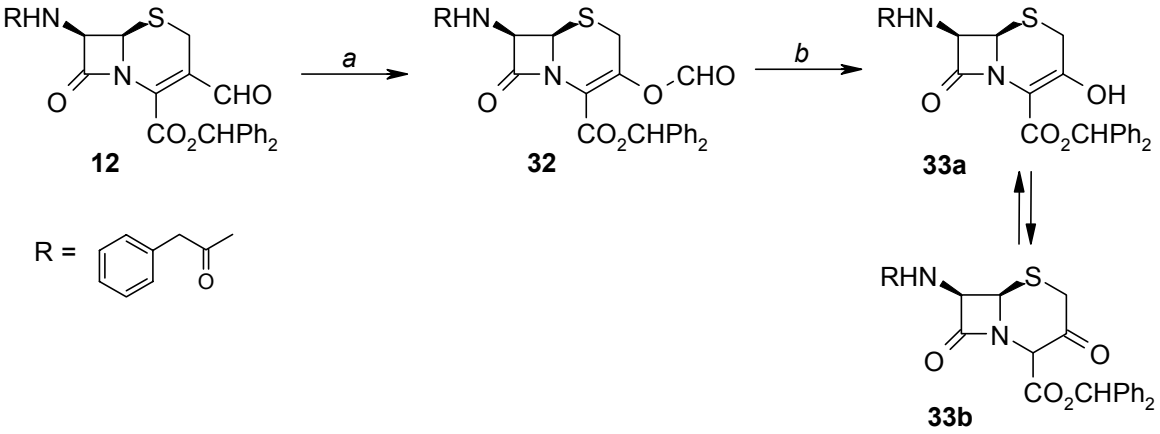
Aldehydes **11** and **12** were successfully decarbonylated with Wilkinson's catalyst (*tris*-triphenylphosphosphine rhodium chloride) in benzene at reflux temperature, affording the parent cephalosporin skeletons **30** and **31** in excellent yields of 80-90% (Scheme 10).[1] Also platinum metal complexes, capable of taking up carbon monoxide, were used for this purpose.[18]



a) Wilkinson's catalyst, benzene, reflux.

Scheme 10.

A second method for removing the formyl-group at C_3 involves a Baeyer-Villiger reaction (Scheme 11).[19] 3-Formylcephalosporins **12** was treated with a peracid and the resulting 3-formyloxycephem **32** was converted into 3-hydroxycephem **33** by hydrolysis, preferably in the presence of a basic agent.

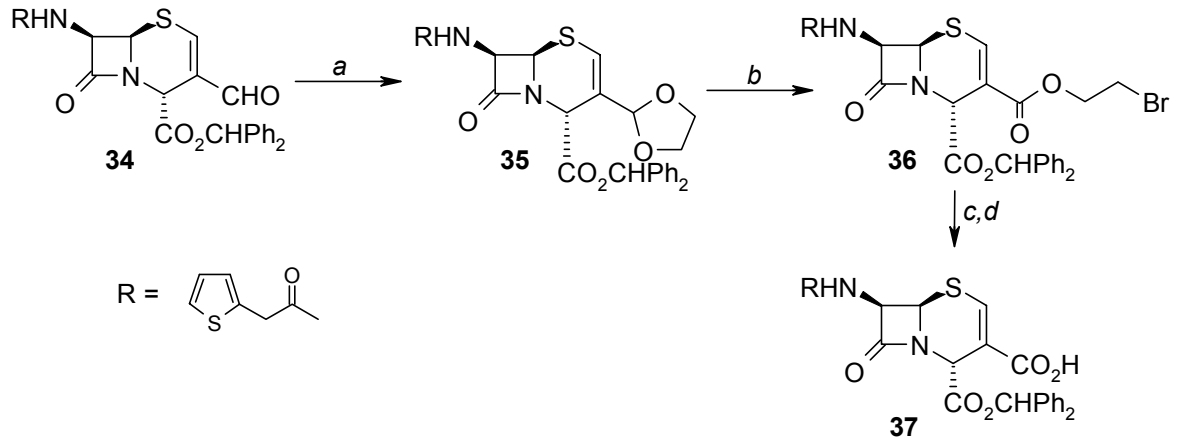


a) peracid; b) H_2O, base.
Scheme 11.

The thus formed cephalosporin **33**, in principle, can be used for the synthesis of the commercially important *β*-lactam antibiotic cefaclor. For this purpose, the hydroxyl group at C_3 is substituted by a chlorine, *e.g.* with PCl_5. Depending on the nature of the peracid, also the corresponding S-oxide has been isolated as a byproduct.

2.5 Oxidation of the 3-formyl group: synthesis of 3-carboxycephalosporins

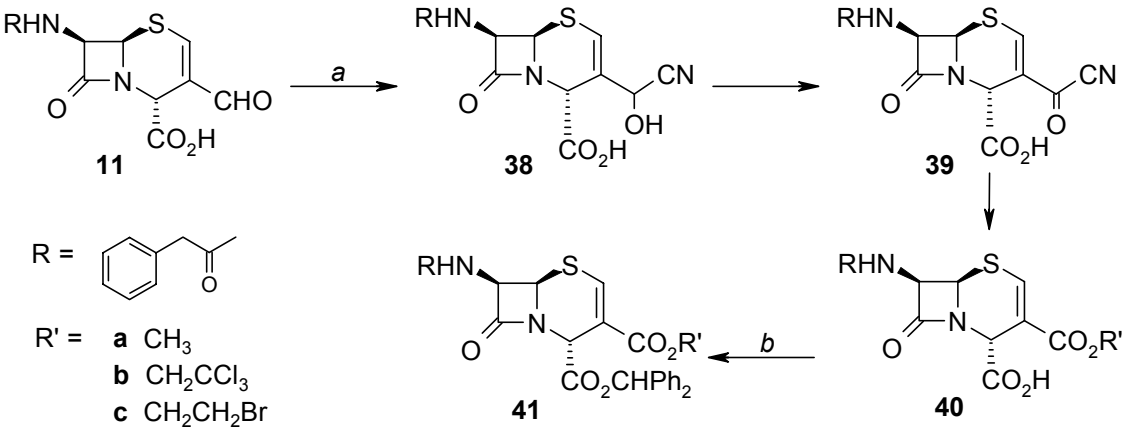
The conversion of the 3-formyl group into the 3-carboxy group is not as straightforward as it seems, as the first synthesis reported involves at least four separate steps (Scheme 12).[20] Reaction of 3-formylcephalosporin **34** with ethylene glycol gave **35** in quantitative yield. Treatment of this ethylene acetal **35** with NBS under radical conditions gave *β*-bromoethyl ester **36** in 45-55% yield, which was converted into the corresponding *β*-iodoethyl ester in a reaction with sodium iodide in acetone in 95% yield. Finally, hydrolysis of the *β*-iodoethyl ester with zinc in acetic acid, gave 3-carboxyceph-2-em **37**.



a) ethylene glycol, acid; b) NBS, AIBN; c) NaI, acetone; d) Zn, acid.

Scheme 12.

Substituted esters of 3-carboxycephalosporins have also been obtained directly from aldehyde **11** (Scheme 13).[21] Treatment of **11** with of a catalytic amount of sodium cyanide afforded the cyanohydrin **38**. Subsequent *in situ* oxidation of **38** with manganese(IV) oxide gave intermediate **39**, which in the presence of the appropriate alcohol released cyanide to produce esters **40a-c**. Protection of the C_4 carboxylic acid function with diphenyldiazomethane gave esters **41a-c** in overall yields ranging from 36 to 79%.



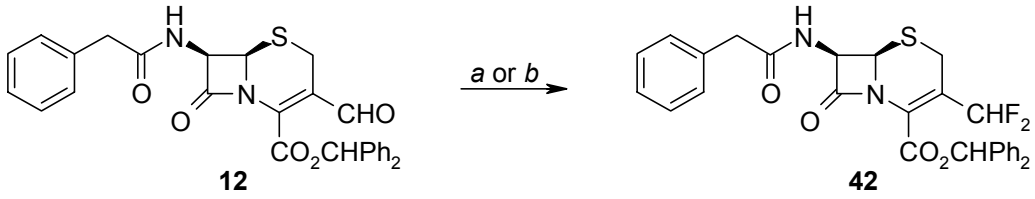
a) NaCN, R'OH, MnO_2; b) Ph_2CN_2.

Scheme 13.

The bromoethyl ester **41c** can be used as an advanced intermediate in the synthesis of 3-carboxycephems, as has been illustrated in Scheme 12 (*vide supra*).

2.6 3-Formylcephalosporins as intermediates in the synthesis of fluorinated compounds

In the synthesis of fluorinated cephalosporins, 3-formylceph-3-em **12** has been used as the key-intermediate (Scheme 14).[22]



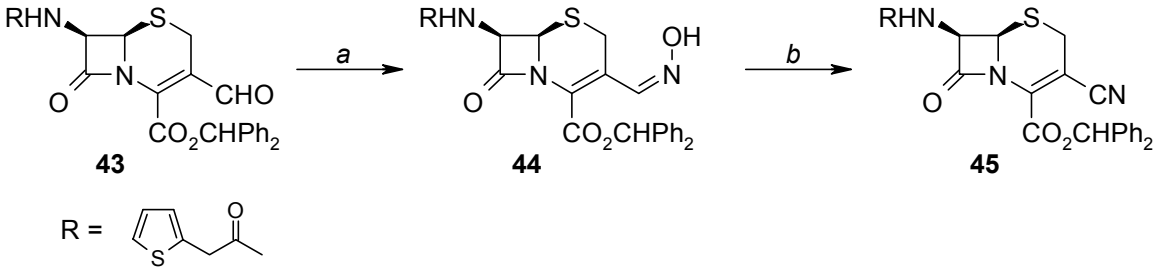
12 **42**

a) piperidinosulfur trifluoride; b) diethylaminosulfur trifluoride.
Scheme 14.

Aldehyde **12** was treated with an excess of piperidinosulfur trifluoride (PST) or diethylaminosulfur trifluoride[23] at room temperature affording crystalline **42** in a moderate yield of 45%.

2.7 Addition of amine-compounds to 3-formylcephalosporins

Hydroxyl amine is one of the first amine compounds that has been used in a reaction with 3-formylcephalosporins. In the past, the reaction of hydroxylamine with *β*-lactam antibiotics, which generally results in rapid cleavage of the *β*-lactam ring, was used as a chemical assay method.[24] Nevertheless, aldehyde **43** could be converted into the corresponding aldoxime **44** in 29% using hydroxylamine (Scheme 15).[25]



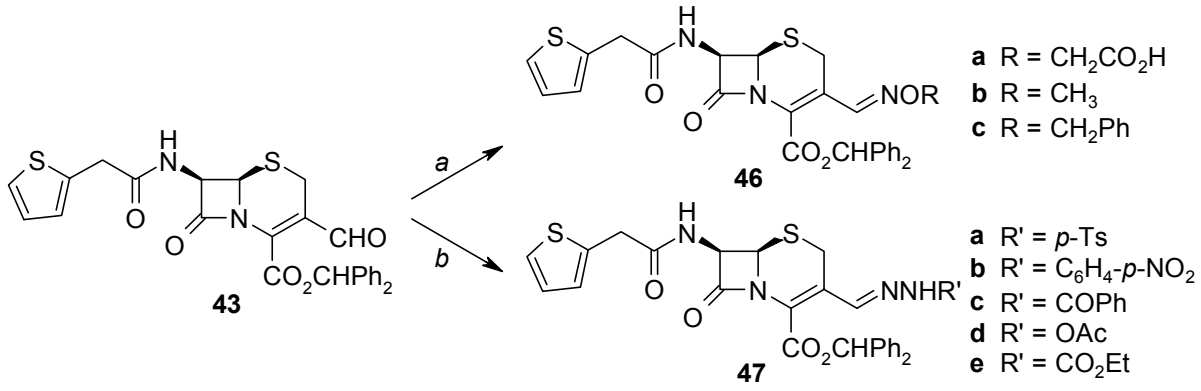
43 **44** **45**

a) NH_2OH; b) $SOCl_2$.
Scheme 15.

The oxidation level of **44** was raised by simply dehydrating the oxime with thionyl chloride to give nitrile **45** in 30% yield. Later, this approach was applied essentially in the same manner to accomplish the synthesis of 3-cyanoceph-3-ems with different side chains (R = phenylacetyl, D-*N*(Boc)-phenylalanin, or 1-hydroxyethyl).[21] The

free acid of **45**, obtainable after removal of the benzhydryl ester, undergoes facile hydrolytic opening of the *β*-lactam ring upon raising the pH above 7.8.

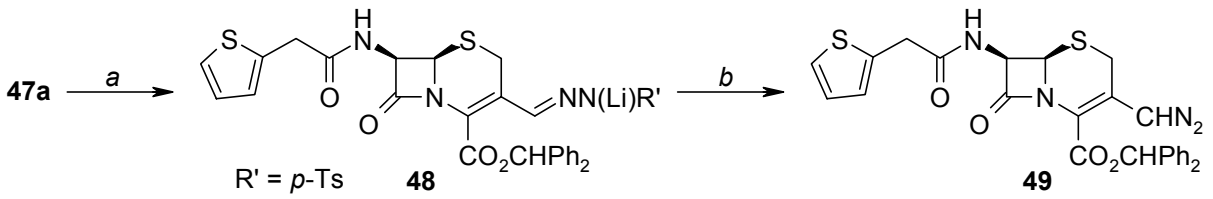
In essentially the same manner, reaction of aldehyde **43** with aminooxyacetic acid hemihydrochloride produced cephem **46a** in 87% yield (Scheme 16). Analogously, formation of oximes **46b** and **46c** was achieved in ca. 50% yield by condensation of **43** with methoxyamine or benzyloxyamine, respectively.[25] With other protection groups at the 7-aminogroup (*e.g.* phenylacetyl or *N*(Boc)-phenylalanine) the reaction with methoxyamine gave similar yields.[21] 3-Formylcephalosporins containing a free carboxylic acid at C_4, were also converted into the corresponding amino-3-oxyiminomethyl-3-cephalosporins in good yields.[26]



a) H_2NOR; b) H_2NNHR'.
Scheme 16.

Substituted hydrazines also add to **43** under carefully chosen conditions. They should be nucleophilic enough to react with the 3-formyl substituent and yet not too basic to rupture the *β*-lactam ring.[27] Thus, an equimolar solution of the aldehyde and *p*-tosylhydrazine in chloroform afforded *p*-tosylhydrazone **47a** in quantitative yield (Scheme 16).[28] This reaction is generally applicable and cephems **47b-e** have been prepared in 30-66% yield using the appropriate hydrazines. Analogously, 3-formylcephalosporins with a free carboxylic acid function at C_4 also react with substituted hydrazines to the corresponding 3-hydrazonocephalosporins.[29]

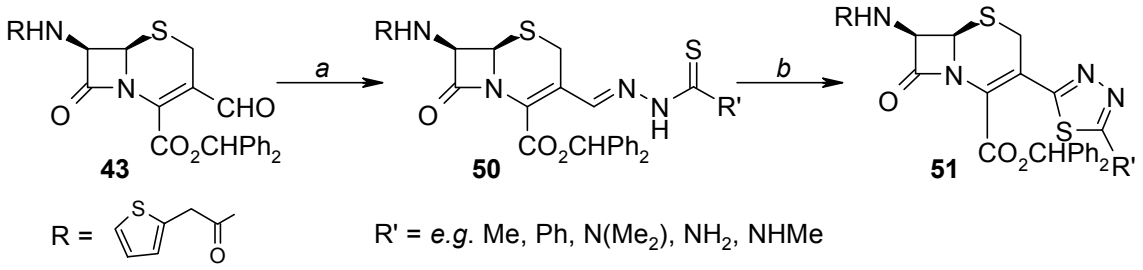
Tosylhydrazone **47a** was used for the preparation of 3-diazomethylcephalosporin **49**. For this purpose, a solution of tosylhydrazone **47a** in THF was brought into reaction with *n*-butyl lithium to give lithium salt **48**. On slowly warming to 40°C, 3-diazomethylcephem **49** was formed in 66% yield (Scheme 17).[28] This reactive cephalosporin undergoes 1,3-dipolar cycloaddition reactions with a large variety of alkenes.



a) n-BuLi, THF; b) 40°C.

Scheme 17.

Analogously, cephalosporins with a thiadiazole unit directly attached to the C_4-position have been synthesized as shown in Scheme 18.[30]

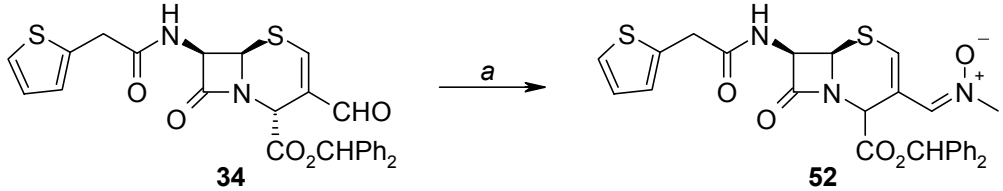


a) $H_2NNHC(S)R'$, DMSO; b) DDQ.

Scheme 18.

Treatment of aldehyde **43** with thiocabonylhydrazines in DMSO led to the corresponding thiocarbonylhydrazones **50** in quantitative yields. Subsequently, oxidative ring-closure by treatment with DDQ in dioxane gave the thiadiazoles **51** in high yields of 71-93%. The use of conventional reagents like $FeCl_3$ or peroxides often led to side reactions.

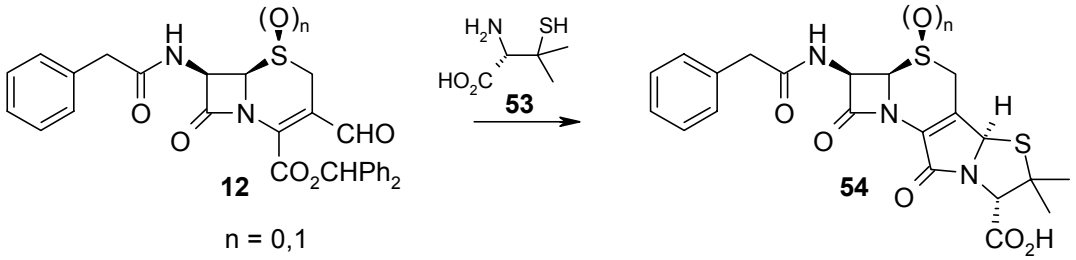
The use of cephem-*N*-methylnitrone **52** as a building block for more complex heterocyclic systems was studied by Spry *et al.*[31] The synthesis of these nitrone involves the use of 3-formylcephem **34** (Scheme 19). Treatment of **34** with N-methylhydroxylamine gave the N-methylnitrone **52** in a moderate yield of 54-64%. Oxidation of **52** to the corresponding sulfoxide, followed by cycloaddition reactions, yielded more complicated tricyclic cephalosporins.



a) CH_3NHOH, pyridine, EtOH.

Scheme 19.

When aldehyde **12** or its sulfoxide was condensed with D-penicillinamine (**53**) in a methanol-chloroform solvent mixture, complex fused tetracyclic systems **54** were obtained, and the benzhydryl group was eliminated (Scheme 20).[32]

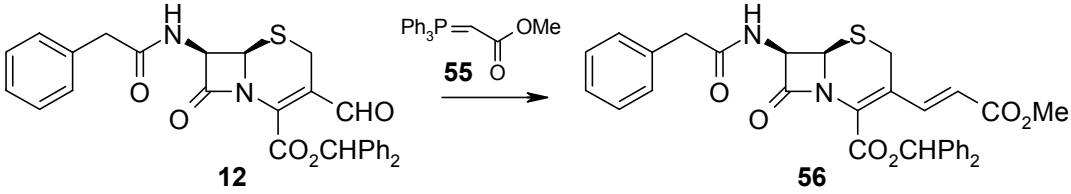


Scheme 20.

When the methyl ester of D-penicillinamine (**53**) was used, the formyl group and the *β*-lactam ring acted as competing reacting centers in this reaction, and therefore, a mixture of products was obtained. This phenomenon can readily be explained by an enhanced nucleophilicity of the D-penicillinamine when present as the methyl ester.

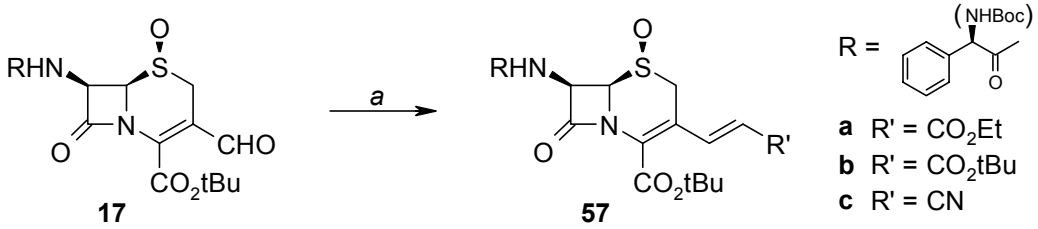
2.8 3-Formylcephalosporins in Wittig reactions

3-Formylcephalosporins only reacted smoothly in Wittig olefination reactions when stabilized phosphoranes were used. Thus, *trans* methyl ester **56** was prepared in 44% yield by reaction of **12** with the stabilized phosphorane **55** (Scheme 21).[33]



Scheme 21.

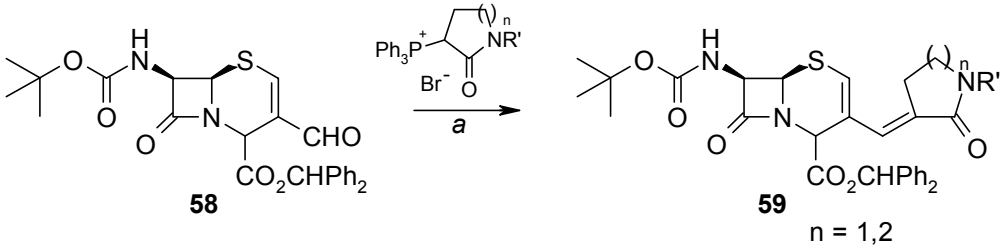
Analogously, 3-formylcephalosporin-S-oxides **17** was subjected to Wittig reactions with a variety of stabilized phosphorous ylides, giving the corresponding 3-(substituted) vinyl-cephem nuclei **57a-c** in reasonable yields (Scheme 22).[7]



a) $Ph_3P{=}CHR'$.

Scheme 22.

Less stabilized phosphoranes have to be prepared *in situ* and were used in an epoxide (1,2-epoxybutane) mediated Wittig reaction with Δ^2-aldehyde **58** to give *γ*- and *δ*-lactamyl derivatives **59** in reasonable yields (Scheme 23).[34] Under these conditions only minor amounts (5%) of the *Z*-derivatives along with small amounts of the corresponding Δ^3-products were formed as well. The corresponding Δ^3-isomers were obtained by an oxidation-reduction sequence involving the ring sulfur atom.

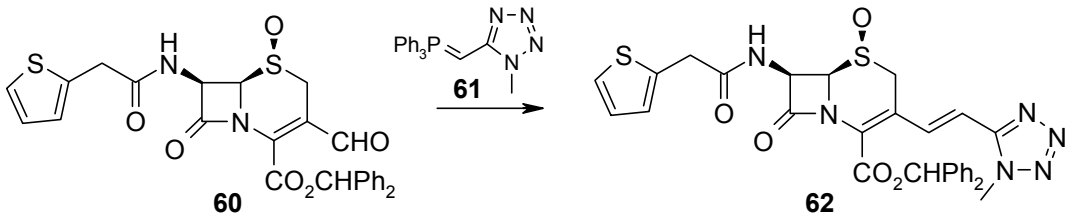


a) 1,2-epoxybutane, 1,2-dichloroethane.

Scheme 23.

The same reaction has also been performed with the corresponding S-oxide of **58**, avoiding the formation of Δ^2/Δ^3-mixtures, which are frequently obtained in the Wittig olefination reaction.[35] For an anti-bacterial activity, however, reduction to the sulfide is always necessary.

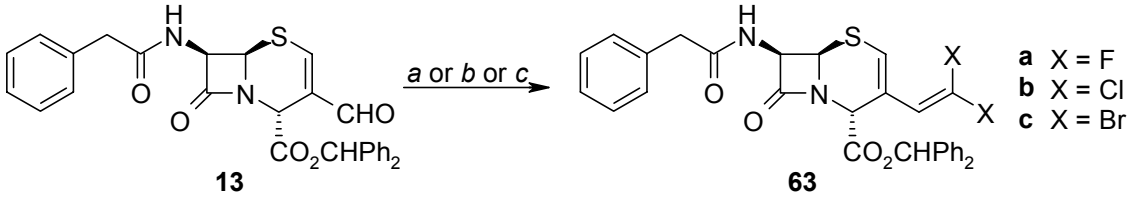
Hashimoto *et al*.[36] used stable phosphorane **61** in THF at a temperature below 0°C in a Wittig reaction with aldehyde **60** to produce alkene **62** (Scheme 24).



Scheme 24.

Higher temperatures caused a significant drop in yield of the olefination products. This Wittig reaction has also been used for the synthesis of other complicated substituted 3-vinylcephalosporins.[37]

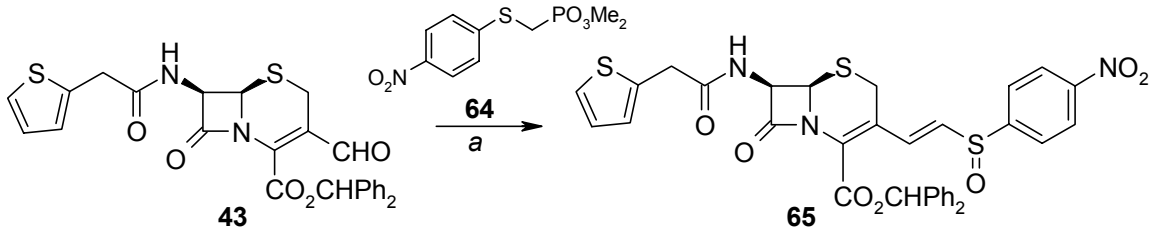
Cephalosporins with a dihalovinyl group at the 3-position have been synthesized in a Wittig-like reaction with aldehyde **13** in poor yields (Scheme 25).[38] The fluorine **63a** derivative was prepared in 10% yield using hexamethylphosphorous triamide as the solvent, zinc powder and dibromodifluoromethane.



a) hexamethylphosphorous triamide, Zn, CBr_2F_2; b) CCl_4, Ph_3P, Zn; c) CBr_4, Ph_3P, Zn.
Scheme 25.

Carbon tetrachloride or carbon tetrabromide, triphenylphosphine and zinc powder gave in a similar reaction the corresponding chlorine- **63b** or bromine-derivative **63c** in 13% and 33% isolated yield, respectively.

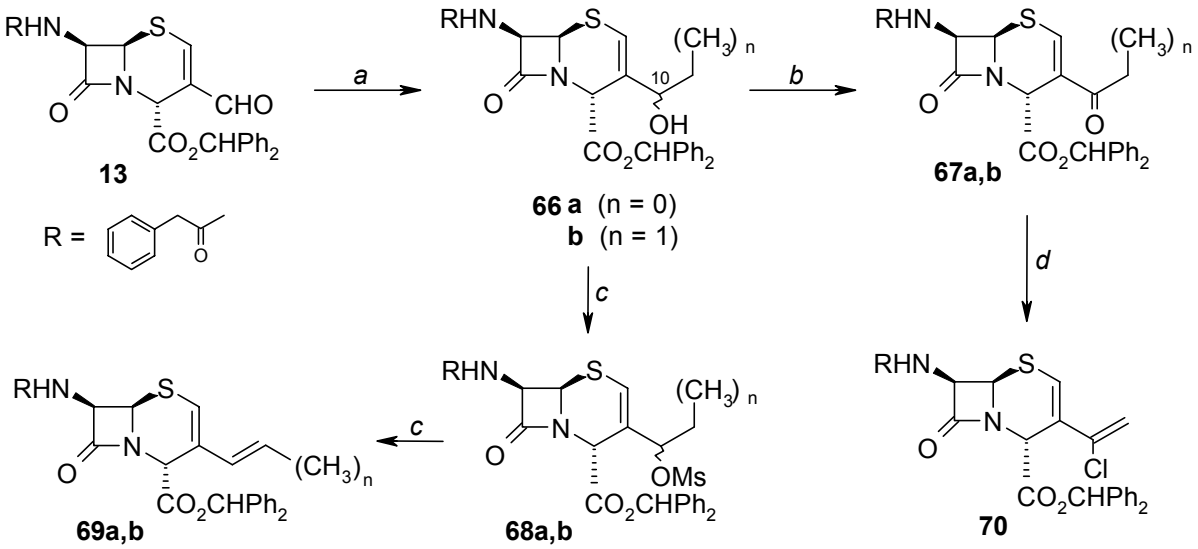
Alkenylsulfoxides **65** can act as enzyme inhibitors, especially of transpeptidase and *β*-lactamase (Scheme 26).[39] These antibacterial agents have been synthesized from 3-formylcephalosporins (*e.g.* **43**) by reaction with dimethyl-*p*-nitrobenzylphosphonate **64** and *n*-butyl lithium in a Wittig-type reaction involving a phosphorous ylide as the reactive species. Simultaneously, the thioether was oxidized to the corresponding sulfoxide in an intra-molecular fashion.



a) n-BuLi, THF.
Scheme 26.

2.9 Grignard reactions with 3-formylcephalosporins

Grignard reactions with 3-formylcephalosporins are well studied and widely used by many groups for the synthesis of 3-functionalized cephalosporins. For example, the Grignard reaction of **13** with MeMgI-LiCl in THF, followed by Jones oxidation of the methylcarbinol intermediate **66a** afforded ketone **67a** in 65% yield from aldehyde **13** (Scheme 27).[40] Lithium chloride is necessary to obtain the carbinol **66a** in high yield.[41] The lithium cation is very effectively coordinated to the oxygen atom of the carbonyl group and thus preventing lactonization.

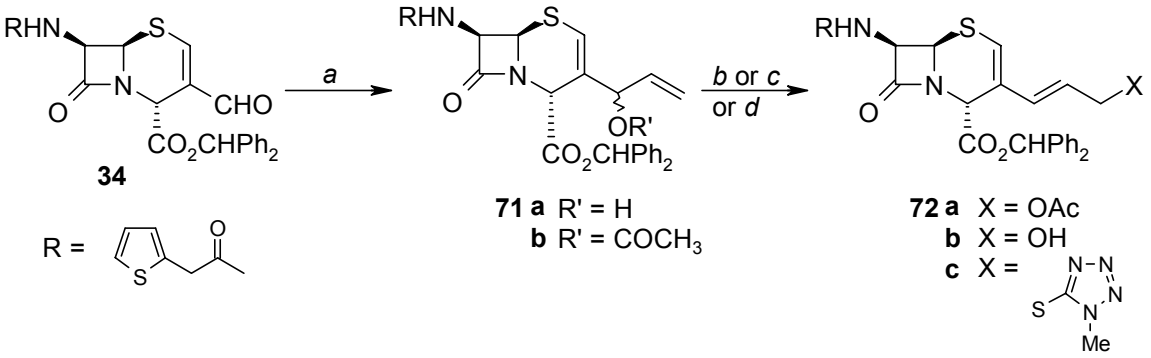


a) MeMgI or EtMgI, LiCl; b) CrO_3, H_2SO_4; c) MsCl, collidine, LiCl, DMF; d) Ph_3P, CCl_4.
Scheme 27.

Dehydration was performed by *in situ* formation of the mesylate **68a** and subsequently elimination using lithium chloride to give the corresponding 3-vinylcephem **69a** in 38% yield.[42] Similarly, addition of ethylmagnesium iodide, followed by dehydration, gave the corresponding 3-(*E*)-1-propenyl cephem **69b** in 40% yield. The ketone group of **67a** has also been converted into an α-chlorovinyl group by treatment with triphenylphosphine in CCl_4 to give compound **70** in 15% yield (Scheme 27).[43]

An elegant example using the Grignard reaction for the modification of the substituent at the C_3 position was reported by Beeby *et al*.[44] Aldehyde **34** was allowed to react with an excess of vinylmagnesium chloride at -70°C to give vinylcarbinol **71a** as a (1:1) mixture of diastereomers. Allylic substitution was achieved with acetic acid using a catalytic amount of *p*-TsOH, thereby producing

acetoxy derivative **72a** in 44%. Similarly, treatment with 5-mercapto-1-methyltetrazole and *p*-TsOH as the catalyst led to thioether **72c** in 66% (Scheme 28).

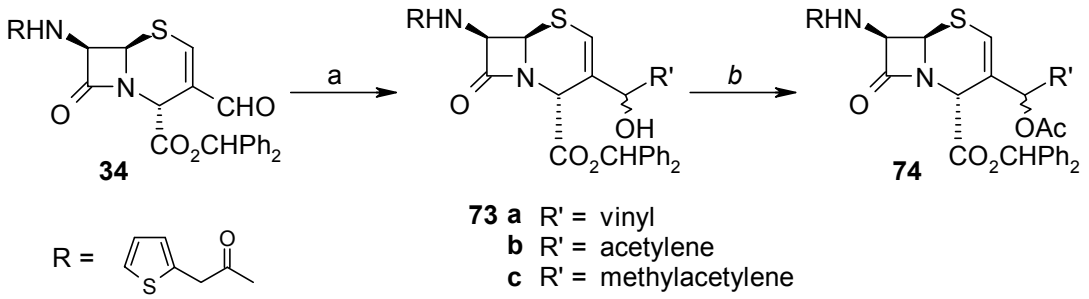


a) vinylmagnesium chloride; b) p-TsOH, THF, AcOH; c) 10% aqueous THF, p-TsOH; d) p-TsOH, 5-mercapto-1-methyltetrazole.

Scheme 28.

Instead of *p*-TsOH, other acids such as perchloric or hydrochloric acid were found to be similarly effective. The corresponding acetate **71b**, obtained by treating **71a** with pyridine and acetic acid anhydride, served equally well as starting material in the abovementioned reactions. Isomerization of **71a** to the primary alcohol **72b** was effected in a similar way using 10% aqueous THF with *p*-TsOH as the catalyst. Conversion of the Δ^2- into the Δ^3-isomers is achieved either by direct equilibration with a trace of triethyl amine in pyridine, or by the two-step oxidation-reduction sequence *via* the sulfoxide intermediates.

Valcavi *et al*..[45] used the Grignard reaction to synthesize novel C_3-substituted cephalothin derivatives from aldehyde **34** (Scheme 29). The corresponding carbinols **73a-c** were acetylated with acetyl chloride in pyridine to give **74a-c** in an overall yield of 36-47%. Ethynylmagnesium bromide was used before to synthesize C_3-propyn-1'-ol cephalosporin **73b**.[46]

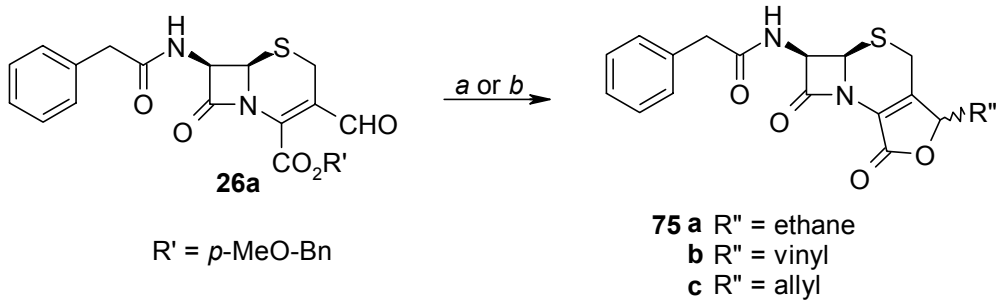


a) R'MgBr; b) AcCl, pyridine.

Scheme 29.

2.10 Barbier-type allylation reaction with 3-formylcephalosporins

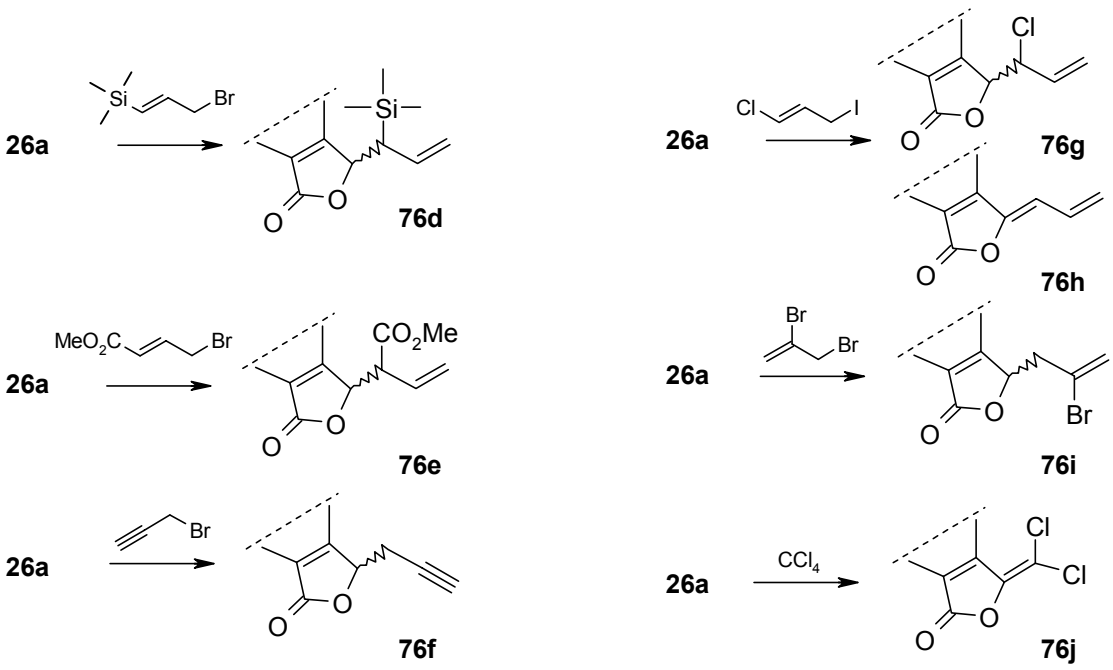
The behavior of aldehyde **26a** in Grignard reactions was also studied by Tanaka *et al*..[47] Ethylmagnesium bromide in THF gave only 14% of the desired product **75a** together with several by-products (Scheme 30). It should be noted that vinylmagnesium bromide did not give an acceptable amount of adduct **75b** (R" = $CH=CH_2$). In contrast, the "Barbier Type" reaction of aldehyde **26a** with allyl bromide in a $PbBr_2$/Al (0.03/1 equivalent)-DMF system proceeded smoothly to produce the desired adduct **75c** in 69% yield. The formation of **75a-c** can be reasonably understood by assuming that the addition of *in situ* generated allylmetal reagents is followed by lactonization.



a) R"MgBr, THF; b) allyl bromide, $PbBr_2$/Al, DMF.

Scheme 30.

In a similar manner, the "Barbier Type" reaction of aldehyde **26a** with other substituted allyl halides and propargyl bromide gave the corresponding functionalized lactones **76d-j** in 33-91% yield (Scheme 31).



Scheme 31.

2.11 Concluding remarks

This overview of synthesis and applications of 3-formylcephalosporins clearly demonstrates the usefulness of this key-intermediate in cephalosporin chemistry. Several research groups actively contributed to this chemistry. It should also be noted that many reactions have been included in patents, indicating the industrial relevance of the chemistry of 3-formylcephalosporins.

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3 AN EVALUATION OF SYNTHETIC ROUTES TOWARDS 3-FORMYLCEPHALOSPORINS

3.1 Introduction

Although nature itself is capable of synthesizing 3-formylcephalosporins,[1] the first man-designed synthesis of a 3-formylcephalosporin (Figure 1) was reported by Woodward *et al*.[2] in 1966, who used the aldehyde as a crucial intermediate in the total synthesis of cephalosporin C. Ever since, many other procedures have been reported. Most of these routes involve a two-step process in which deacetylation of the 3-acetoxy group in a 7-ACA analogue is followed by oxidation of the thus obtained hydroxymethyl group into the aldehyde function. Some stoichiometric oxidations used are the Moffat oxidation,[3] the Collins oxidation,[3] and the Jones oxidation.[3],[4] Manganese(IV) oxide,[3],[5] and chromium(VI) oxide in acetic acid[3] have also been applied. In one report, the Swern oxidation has been used.[5] Recently, more elegant methods were published, employing 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX)[6] in DMSO, and the catalytic method using TEMPO[7] in combination with a co-oxidant.

Part of this chapter has been published: Keltjens, R.; Vadivel, S.K.; De Vroom, E.; Klunder, A.J.H.; Zwanenburg, B., *Eur. J. Org. Chem*. **2001**, 2529.

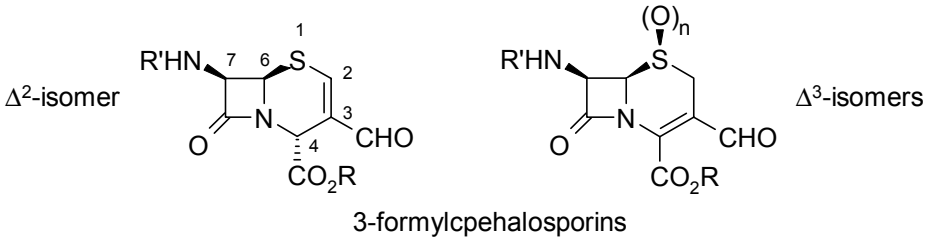


Figure 1.

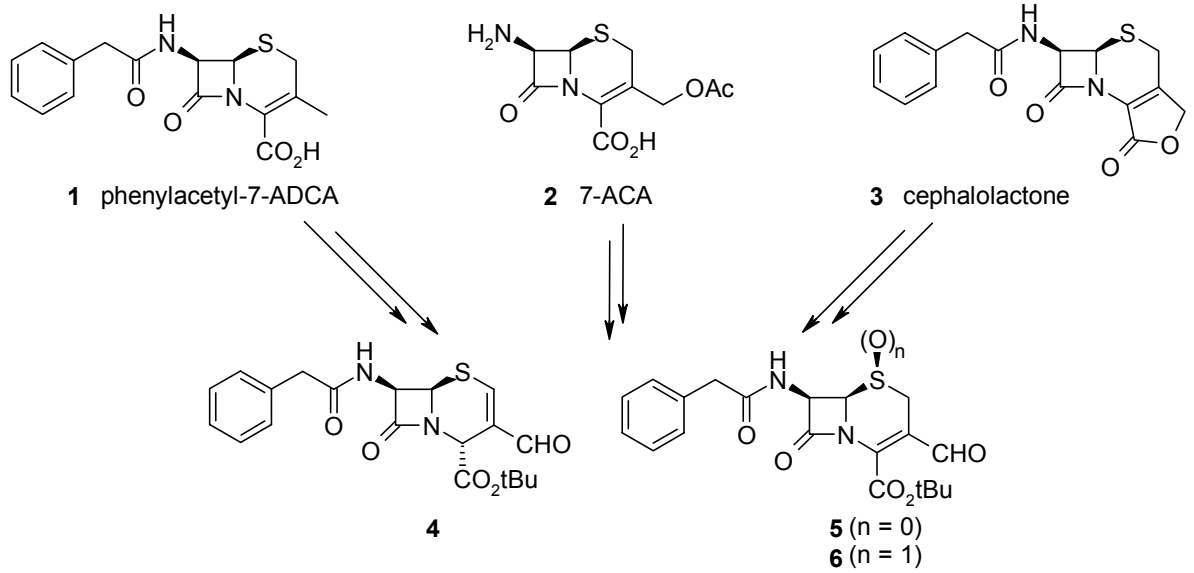
Other oxidations of 3-iodomethylcephalosporins, which involve oxygen- or air oxidation[8] either in the presence of rhodium(III) chloride or phosphomolybdic acid,[9] are also known. In an alternative non-oxidative approach, 3-formylcephalosporins are synthesized from the readily available cephalosporin lactones.[10] A more comprehensive and detailed overview of the synthesis and applications of 3-formylcephalosporins has been described in chapter 2.

3-Formylcephalosporins have great potential as synthetic intermediates, as they allow either the synthesis of a variety of new β-lactam antibiotics, or a new synthetic route to cephalosporins, which are already on the market for many years. The presence of the formyl group is essential, as it can serve as a handle for the introduction of numerous new functionalities. Since no general synthesis of 3-formylcephalosporins was available at the start of this study, it was considered relevant to design a new synthetic route to this aldehyde, based on modern synthetic concepts. Such a synthetic effort is in full accordance with the objective formulated at the outset of the project, namely synthetic manipulation at the C_3 position in cephalosporins in order to improve existing synthetic procedures to known antibiotics, and also to provide access to novel biologically promising cephalosporin entities.

Such a new synthetic route has to fulfill three requirements. In the first place, the synthesis must start from readily available and cheap materials. Secondly, the synthetic route should be as short as possible and be high yielding as well. Finally, all possible isomers with respect to the position of the double bond and the oxidation state of the sulfur atom should be easily accessible *via*, at least in principle, the same procedure.

This chapter is an evaluation of synthetic approaches to 3-formylcephalosporins **4-6** implied in this study. Three readily available cephalosporins, *viz*. phenylacetyl protected 7-aminodesacetylcephalosporanic acid (7-phenylacetyl-ADCA) **1**, 7-

aminocephalosporanic acid (7-ACA) (**2**), and cephalolactone **3** were selected as starting materials (Scheme 1). These compounds are readily available from fermentation and are industrially attractive starting compounds.

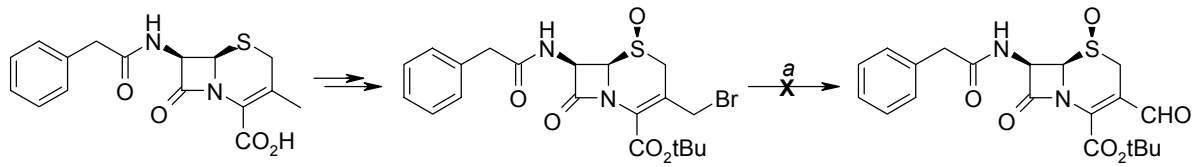


Scheme 1.

3.2 Results and discussion

3.2.1 Synthesis of 3-formylcephalosporins from 7-ADCA

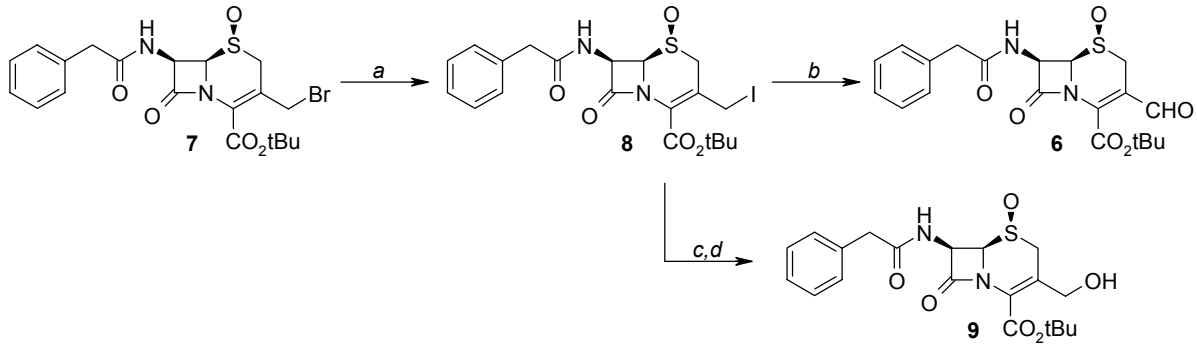
7-Phenylacetyl-ADCA **1** is an interesting candidate for the synthesis of 3-formylcephalosporins, as it is readily available in industrial quantities from penicillin G fermentation followed by ring-expansion (Scheme 2). 7-Phenylacetyl-ADCA was used as such, as there is no need to deprotect the 7-amino function, because this unit can easily be deprotected enzymatically at a later stage.[11] For the required protection of the C_4-carboxyl group the *tert*-butyl ester was chosen, because this environmentally benign and economically interesting group can be readily introduced. Moreover, the re-conversion of the esters into the corresponding carboxylic acids, which in general is rather problematic for these types of substrates, is high yielding in the case of the *tert*-butyl ester.[12]



a) $AgBF_4$, Et_3N, DMSO, r.t., 15h.

Scheme 2.

Oxidation of the sulfide to the corresponding sulfoxide and allylic bromination with *N*-bromosuccinimide under radical conditions, gave bromomethyl derivative **7** in good yields. The only drawback of the radical bromination step is the formation of by-products due to bromination at the benzylic or the allylic position adjacent to the sulfur atom. For this study, compound **7** was obtained from DSM Anti-Infectives.[13] Consultation of the literature revealed that allylic bromides can be oxidized to the corresponding aldehyde in only one step applying a Swern-type reaction with $AgBF_4$.[14] Unfortunately, this method appeared not suitable for the synthesis of aldehyde **6**. Subjecting **7** to this oxidation procedure afforded a product that, according to ^{1}H-NMR-analysis, did not contain the *β*-lactam ring anymore. Apparently, the reaction conditions are too harsh for this sensitive molecule leading to complete breakdown of the cephalosporin ring system.



a) NaI, acetone, 5h (r.t.) and 2.5h (45°C), 97%; b) O_2, $RhCl_3$ (cat.), Al, DMF, o/n, 23%; c) $CF_3CO_2{\cdot}NH_4$, DMF, 50°C, 2.5h; d) phosphate buffer pH 7.0, 32%.

Scheme 3.

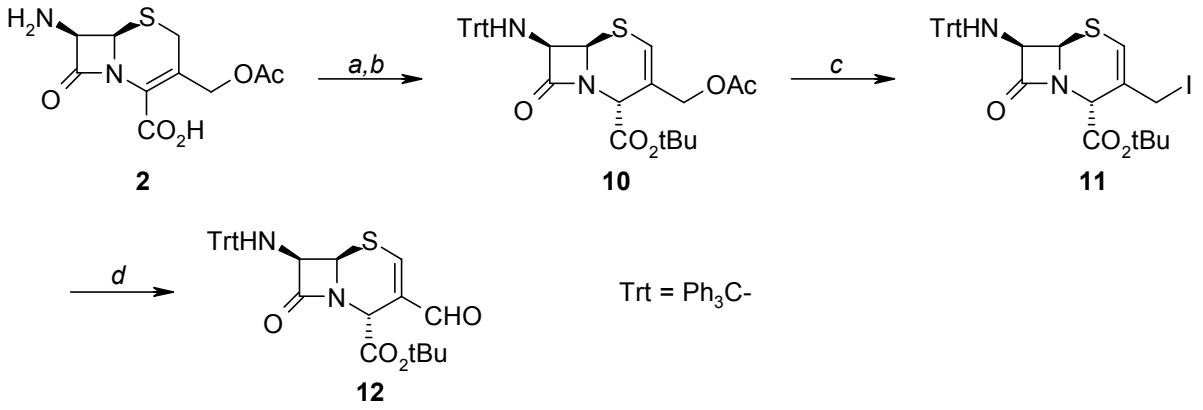
As direct oxidation of bromine **7** turned out to be impossible, iodine analog **8** was prepared in quantitative yield from **7** using sodium iodide in acetone. It has been reported that such cephalosporin methyl iodides can be oxidized to the corresponding aldehydes reasonably efficiently applying oxygen in dimethylformamide and rhodium(III) chloride as the catalyst (Scheme 3).[9] When methyl iodide **8** was subjected to this oxidation procedure, aldehyde **6** was isolated,

albeit in a rather low yield of 23%. Much higher yields were obtained for related methyl iodides containing a *p*-methoxylbenzyl, *p*-nitrobenzyl or diphenylmethyl ester[9] at the C_4 position instead of a *tert*-butyl ester as in **8**. The nature of the C_4-ester substituent apparently plays a role in this direct oxidation of 3-iodomethylcephalosporins to the corresponding aldehydes.

In an alternative approach, iodide **8** was converted into the corresponding alcohol **9** in 32% isolated yield by reaction with ammonium trifluoroacetate in DMF and work-up with an aqueous phosphate buffer (Scheme 3).[15] The actual yield was much higher according to TLC- and ^{1}H-NMR analyses. Purification by column chromatography caused a dramatic loss in yield, probably caused by decomposition at the active surface of the stationary phase. Next, hydroxy compound **9** was subjected to a variety of oxidation procedures in order to obtain the desired aldehyde **6** (*vide infra*).

3.2.2 Synthesis of 3-formylcephalosporins from 7-ACA

In comparison with 7-ADCA (**1**), 7-ACA (**2**) has a major advantage as the starting substance, because it has a higher oxidation state of the C_{10} carbon atom. In compound **2**, an acetoxy group is present at C_{10}, whereas 7-ADCA has a C_3 methyl group. For the preparation of 3-formylcephalosporins, nearly the same strategy as described above in Section 3.2.1. was followed for 7-ACA as the starting material. The required protection of the carboxyl group at C_4 was attained *via* a *tert*-butyl ester function, prepared in the usual way with isobutene and sulfuric acid[16] (Scheme 4). Subsequently, the amino function was protected with trityl chloride using triethyl amine as the base to give *N*-tritylated *tert*-butyl ester **10** in only 13% overall yield. Under these basic reaction conditions the double bond had completely isomerized from the Δ^3- to the Δ^2-position, possibly due to an increased steric interaction between the acetoxy substituent at the C_{10} position and the bulky *tert*-butyl ester at C_4. This is a surprising observation, since generally mixtures of the Δ^2- and Δ^3-isomer are formed.[17],[18] Release of steric interference between the *cis* substituents in the ceph-3-em system may be invoked to explain this phenomenon.[19]

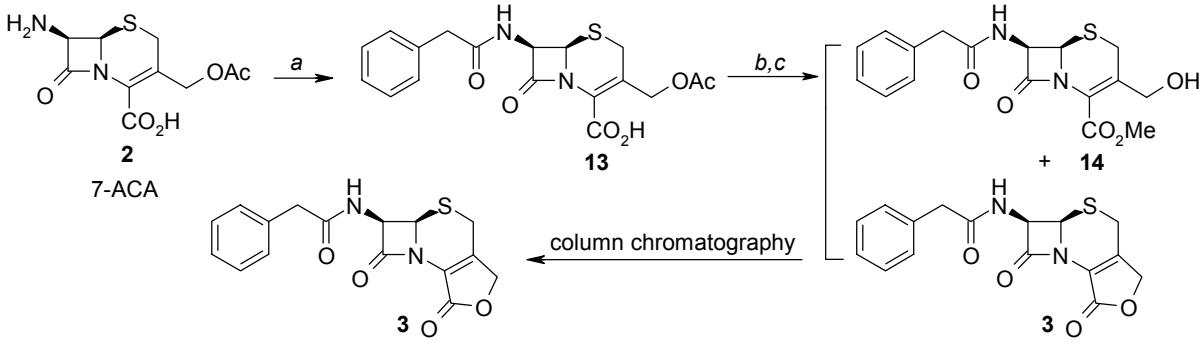


a) isobutene, sulfuric acid (cat.), DME, r.t., 3 days; b) trityl chloride, Et_3N, CH_2Cl_2, r.t., 15h, 13%; c) TMSI, CH_2Cl_2, r.t., 1h, 72%; d) O_2, $VOSO_4$, r.t., 2h, trace.

Scheme 4.

In the next step, the acetoxymethyl group was converted into an iodomethyl group by reacting **10** with trimethylsilyl iodide, followed by aqueous work-up.[20] The resulting iodide **11** was transformed into the 3-formylcephalosporin by catalytic oxidation with oxygen using rhodium(III) chloride or vanadyl sulfate as the catalyst.[9] Unfortunately, this reaction gave aldehyde **12** only in trace amounts. In view of the facts that the yields in both protection steps of 7-ACA were disappointingly low and that the conversion of the iodomethyl group into the formyl moiety was also a low-yielding reaction, the synthetic strategy for the synthesis of 3-formylcephalosporins from 7-ACA was reconsidered.

In the new approach, a phenylacetyl amino protection was chosen as its usefulness had been proven in the 7-ADCA route to 3-formylcephalosporins (see Section 3.2.1). Reaction 7-ACA (**2**) with phenylacetyl chloride under Schotten-Baumann conditions afforded the desired amido compound **13** in an excellent yield of 83% yield (Scheme 5).

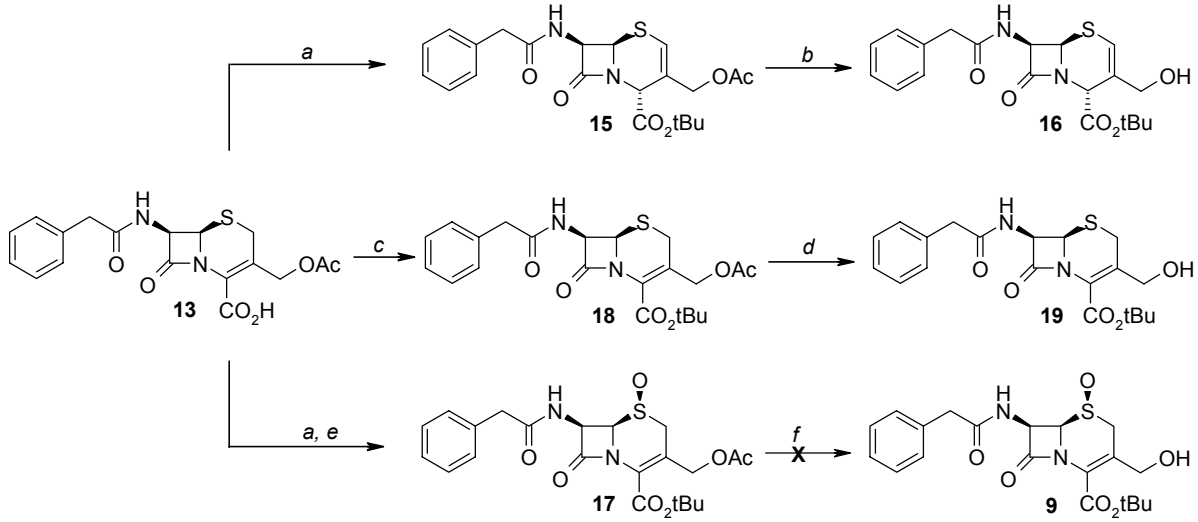


a) phenylacetyl chloride, H_2O pH 8.0, r.t., o/n, 83%; b) NaOH, H_2O / MeOH, -20°C, 30'; c) pH stat 4.5, CH_2N_2, Et_2O, EtOAc, 70%.

Scheme 5.

With the aim to obtain the corresponding alcohol **14**, saponification of the acetoxy unit in **13** was investigated. Reaction with sodium hydroxide in methanol, followed by acidification and subsequent treatment with diazomethane at a constant pH, in order to esterify the 3-carboxylic acid function, led to a mixture of two products according to TLC analysis. On attempts to separate these compounds by column chromatography, only a single product was isolated. Both ^{1}H-NMR spectroscopy and IR analysis indicated the presence of lactone **3**. This exclusive formation can readily be rationalized by lactonization of the intermediate hydroxy methylester **14** catalyzed by the relatively acidic silicagel used for the column chromatography. In a different approach, lactone **3** was evaluated as a precursor for the synthesis of 3-formylcephalosporins (*vide infra*) (see also Chapter 2).

In order to avoid lactonization, the C_4 carboxyl group of **13** was first protected as a *tert*-butyl ester by treatment with dicyclohexyl carbodiimide and *tert*-butyl alcohol using DMAP as the catalyst. The only product obtained, after recrystallization, was the Δ^2-isomer **15** in 88% yield (Scheme 6).



a) DCC, tert-BuOH, DMAP (cat.), CH_2Cl_2, -30°C - r.t., 88%; b) NaOH, MeOH, -20°C, 4h, 98%; c) isourea (DCC, tert-BuOH), CH_2Cl_2, r.t., 15h, 79%; d) NaOH, MeOH, -30°C, 6h, 44%, e) m-CPBA, $CHCl_3$, 0°C, 2h, 98%; f) NaOH, MeOH, -40°C.

Scheme 6.

The synthesis of Δ^3-sulfide **18** was achieved by using the isourea derived from *tert*-butyl alcohol and DCC[21] instead of the DCC/DMAP method. As no base is required in this procedure, only Δ^3-acetoxy ester **18** is formed, and isomerization to the Δ^2-sulfide **15** cannot take place. The corresponding Δ^3-sulfoxide **17** could be synthesized by oxidation of the Δ^2-sulfide **15** with *m*-CPBA in quantitative yield (Scheme 6). On first sight, hydrolysis of the acetoxy function seemed to be

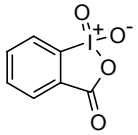
straightforward, but in practice new difficulties were encountered. Saponification of the acetoxy group in **17** with sodium hydroxide in methanol led, immediately after the addition, to severe decomposition of the starting material, even at -40°C. Most likely, nucleophilic opening of the β-lactam ring by the hydroxide ion,[22] initiates this undesired process leading to a black tar in only 30 minutes. Saponification was more successful in the case of the corresponding sulfides **15** and **18**. After 6 hours at -30°C, about 50% of starting material **18** was still present. Addition of an extra equivalent of base did not increase the rate of the hydrolysis. Instead more decomposition of the starting material was observed. As a result hereof, Δ^3-hydroxy compound **19** was only obtained in a moderate yield of 44%. Only for the Δ^2-compound **15** the hydrolysis of the C_{10} acetoxy group appeared to be facile, affording **16** in quantitative yield. This different behavior between **15** and **18** is not yet understood. The remarkable differences between **15**, **17**, and **18** clearly indicate that subtle differences in structure may have enormous consequences for the chemical behavior.

After saponification of the acetoxy group, the primary alcohol was subjected to an oxidation procedure in order to obtain the corresponding aldehyde. For establishing the optimum reagent and reaction conditions, a large number of test reactions was performed with the alcohols **9**, **16** and **19**. The results are collected in Table 1.

The data in Table 1 reveal that the choice of oxidizing reagent is very important. Activated manganese(IV) oxide (entries 1 and 2) gave good results. However, the large excess needed to force the reaction to completion, and the sometimes lower isolated yield caused by sticking of the product to the manganese(IV) oxide, are serious disadvantages. Moreover, the quality of the manganese(IV) oxide, which is very essential, is not reliable. The oxidizing reagents of the chromate family[23],[24] (entries 3-5) did not react or showed a moderate reactivity towards the 3-hydroxymethylcephalosporins. The Moffat oxidation[3] seemed to be successful, but appeared to be a very slow and therefore unpractical reaction. Although the TEMPO catalyzed oxidation of a cephalosporin was described in a patent,[7] the specific examples mentioned in the patent gave non-reproducible results when repeated. Minor modifications, *e.g.* using NCS as co-oxidant did also not lead to positive results.[25] Using other catalysts, *e.g.* platinum(IV) oxide, chromium(VI) oxide[26] and rhodium(III) chloride (entries 13-16) was not successful either, demonstrating the difficulties of the oxidation of the 3-hydroxymethylcephalosporins. Even the well-

known Swern oxidation failed, although in literature one successful example is claimed.[5],[27] Only degradation of the starting material **16** was observed.

Table 1: *Oxidation of the 3-hydroxymethyl group to the 3-formyl group*

entry:	method:	alcohol[a]:	yield: (%)[b]
1	activated MnO_2 (40°C)	**9**	88
2	activated MnO_2 (40°C)	**16**	79
3	benzimidazolium dichromate (BIDC), microwave	**9**	0[c]
4	pyridinium chlorochromate (PCC)	**16**	42
5	isoquinolinium dichromate (IQDC)	**16**	19
6	DMSO, Ac_2O (Moffat)	**16**	n.d.
7	TEMPO (cat.), O_2	**16**	0[c]
8	TEMPO (cat.), NaOCl	**16**	0[c]
9	TEMPO (cat.), NCS	**9**	0[d]
10	IBX	**9**	96
11	IBX = 	**16**	81
12	IBX	**19**	95
13	PtO_2 (cat.), O_2	**9**	0[c]
14	PtO_2 (cat.), O_2	**16**	0[c]
15	CrO_3 (cat.), H_5IO_6	**9**	trace
16	$RhCl_3$ (cat.), $NaIO_4$	**19**	n.d.[e]
17	oxalyl chloride, DMSO (Swern)	**16**	0[f]

[a] **9** = sulfoxide, **16** = Δ^2-sulfide, **19** = Δ^3-sulfide

[b] isolated yield

[c] no reaction; only starting material recovered

[d] chlorinated products; no aldehyde (^{1}H-NMR)

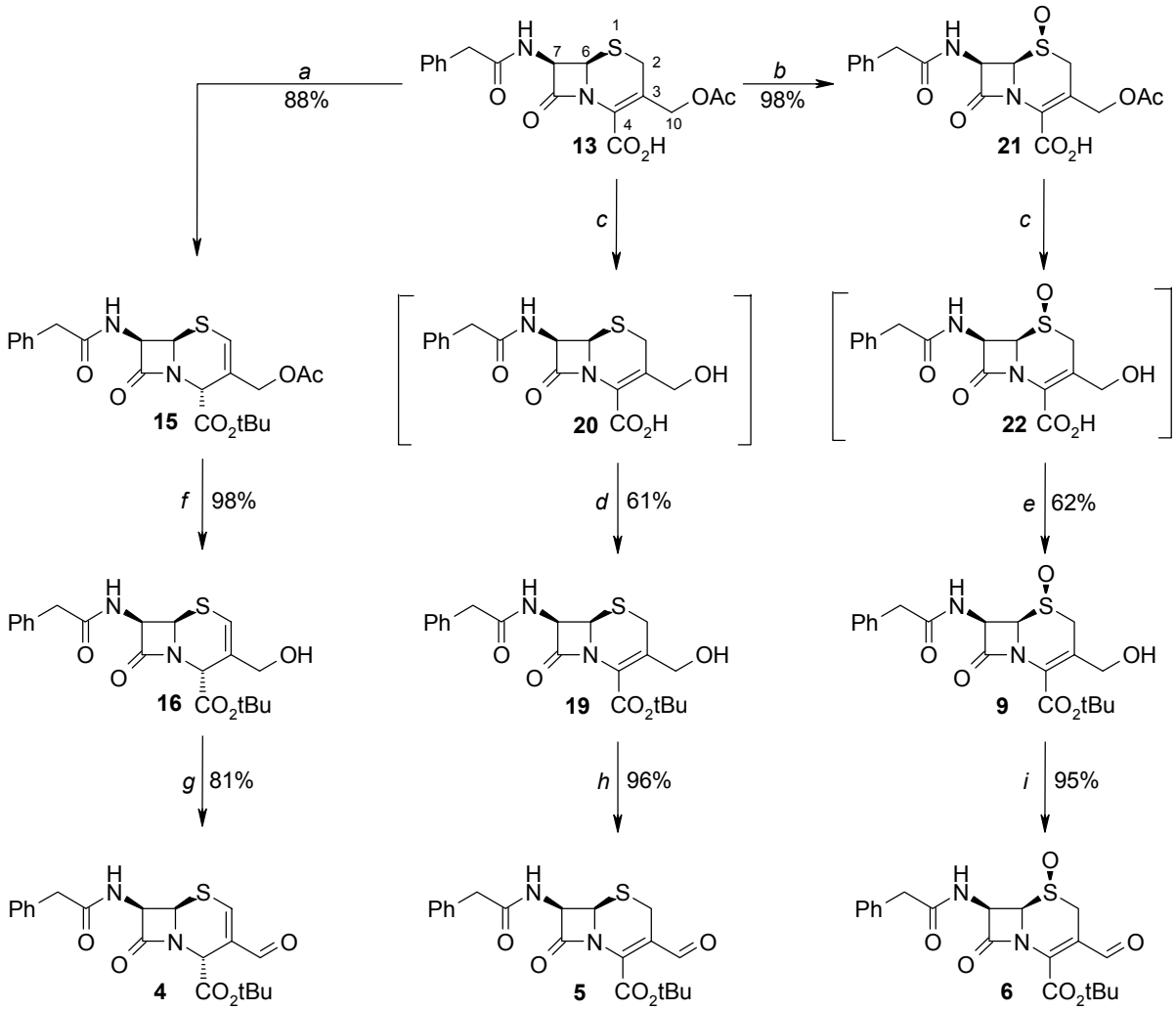
[e] aldehyde, but also over-oxidation to corresponding sulfone

[f] severe decomposition

Most gratifyingly, a modification of the Dess-Martin oxidation, *i.e*. the precursor for the Dess-Martin reagent *i.e*. 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) was successful and gave excellent results (entries 10-12).[6] The corresponding aldehydes were obtained in high yields (81-96%). IBX is one of the mildest reagents available for the oxidation of alcohols to carbonyls. The reagent can easily be prepared on large scale, and it has been claimed that detonation is less probable as compared to the Dess-Martin reagent.[6] Moreover, only 1.5 equivalents were necessary to

complete the oxidation of alcohols **9**, **16**, and **19** in a clean and selective manner in short time.

In summary, the experiments described above show that the conversion of 7-ACA into the 3-formylceph-2-em **4** only involves four steps, all of them high yielding, resulting in overall yields of 47-58%. The sequence of steps to this aldehyde **4** is depicted in Scheme 7 (left column).



a) tert-BuOH, DCC, DMAP (cat.), CH_2Cl_2, -30°C - r.t., o/n, 88%; b) MCPBA, CH_2Cl_2, 0°C, 1.5h, 98%; c) cephalosporin acetyl hydrolase (CAH), H_2O pH 7.5, r.t., 4-8h; d) isourea (DCC, tert-BuOH), THF, o/n, 61%; e) isourea (DCC, tert-BuOH), THF, o/n, 62%; f) NaOH, MeOH, -20°C, 4h, 98%; g) IBX, DMSO/THF, r.t., 30h, 81%; h) IBX, DMSO, r.t., 15', 96%; i) IBX, DMSO, r.t., 15', 95%.

Scheme 7.

The synthesis of the corresponding 3-formylceph-3-em **5** was approached in a similar manner. After protection of the amino group, the acetate at C_{10} was hydrolyzed applying an immobilized enzyme (cephalosporin acetyl hydrolase) to give the hydroxyacid **20** in high yield. This compound has to be handled with great

care to prevent lactonization under acidic conditions (Scheme 5). To avoid the formation of Δ^2 by-products in the next protection step, the esterification of the C_4 carboxylic acid function in **20** was accomplished by treatment with the isourea derived from DCC and *tert*-butyl alcohol[21] to give the *tert*-butyl ester **19** in 62% overall yield. As no base is required in this procedure, only Δ^3-hydroxy ester **19** is formed. Oxidation of alcohol function at C_{10} in **19** to the corresponding aldehyde **5** was achieved in almost quantitative yield with IBX as the oxidizing agent.

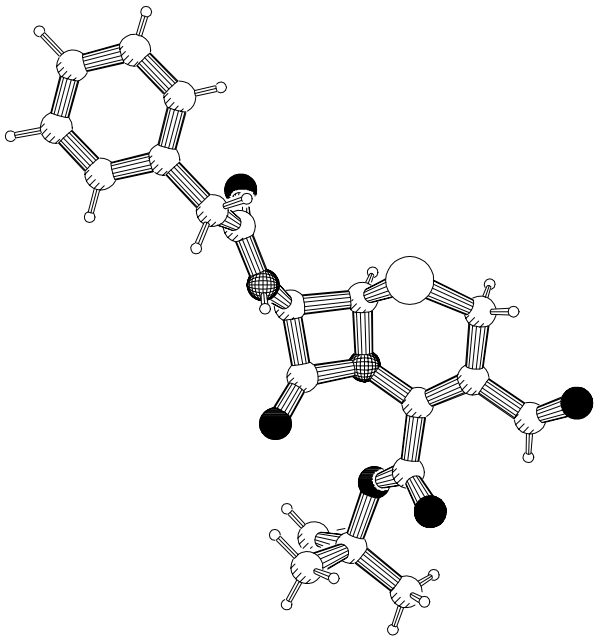
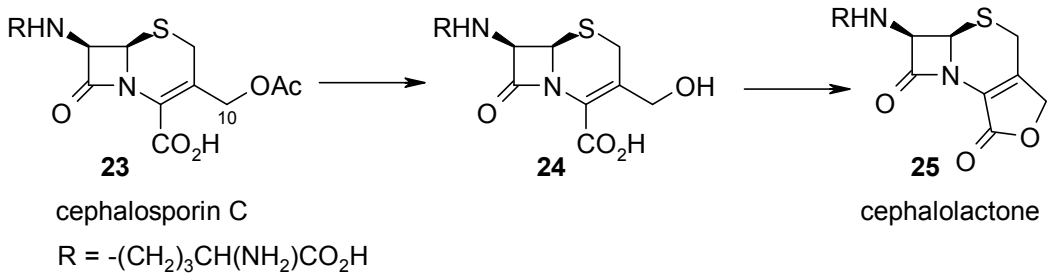


Figure 2. *PLUTON drawing of the X-ray structure of aldehyde* ***5****.*

The synthesis of 3-formylceph-3-em-1-oxide **6** started from sulfide **13**, which was oxidized in quantitative yield to the sulfoxide **21** with *meta*-chloroperbenzoic acid (Scheme 7). Hydroxyacid **22** was obtained by enzymatic hydrolysis (cephalosporin acetyl hydrolase) of the C_{10} acetate in **21**. The *tert*-butyl ester **9** was then obtained from **22** in an overall yield of 61% by treatment with the isourea derived from DCC and *tert*-butyl alcohol. Oxidation of the C_{10} hydroxy function to the corresponding 3-formylcephalosporin **6** was accomplished, again in excellent yield, using IBX as the oxidant. The chemistry shown in Scheme 7 represents efficient novel routes to the aldehydes **4**, **5**, and **6**, which are key-compounds for further synthetic elaboration of the cephalosporin nucleus at C_{10}.

3.2.3 Synthesis of 3-formylcephalosporins from cephalolactone

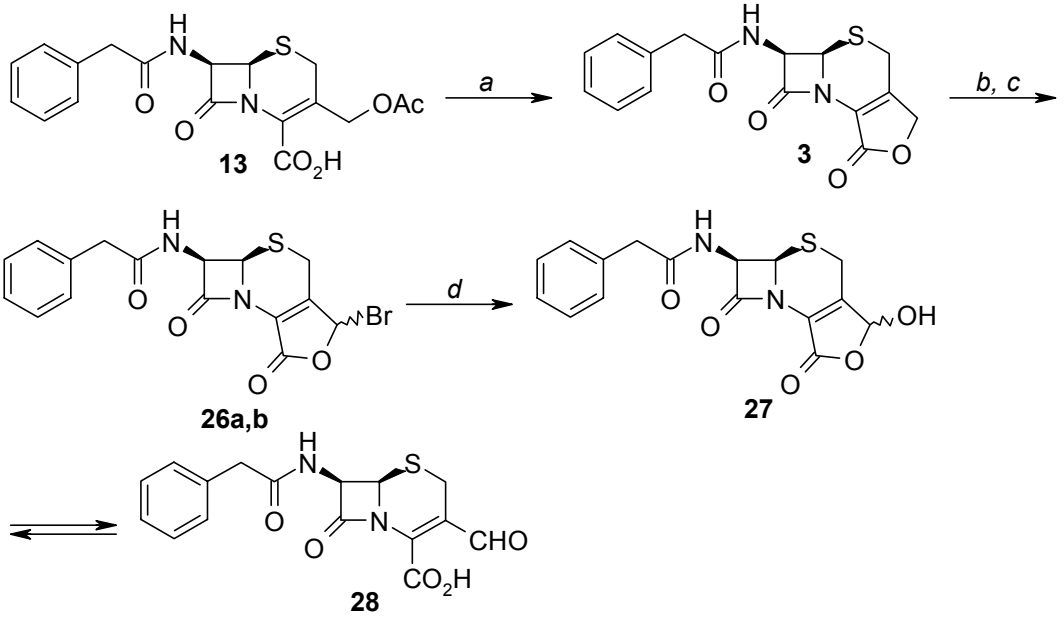
Initially, cephalosporin lactones were not of particular interest from a synthetic point of view. In the early 1960s, the first uncontrolled synthesis of such lactone was reported by Abraham *et al*.[28] In an attempt to deacetylate cephalosporin C (**23**) to the corresponding hydroxyacid **24** under acidic conditions, mainly the lactone **25** was formed (Scheme 8). A more controlled synthesis by Chauvette *et al*.[29] involves the enzymatic deacetylation of **23** with *orange peel acetyl esterase* to give the hydroxyacid **24**, followed by lactonization to cephalolactone **25** in the presence of acid or acetic anhydride. Later, Kukolja *et al*.[30] nicely demonstrated that lactonization without a separate deacetylation step was possible by simply stirring phenylacetyl amino-protected 7-ACA **13** in acidic aqueous acetone (Scheme 9).



Scheme 8.

As already mentioned in the introduction (Scheme 1, for more details see Section 2.2 in Chapter 2), 3-formylcephalosporins can be synthesized from this readily available cephalosporin lactone **3**.[10] The literature procedures were repeated with some adaptations. Thus conversion of phenylacetamide protected 7-ACA **13** into cephalolactone **3** (89% yield) was accomplished by stirring it in aqueous acid and acetone.[30]

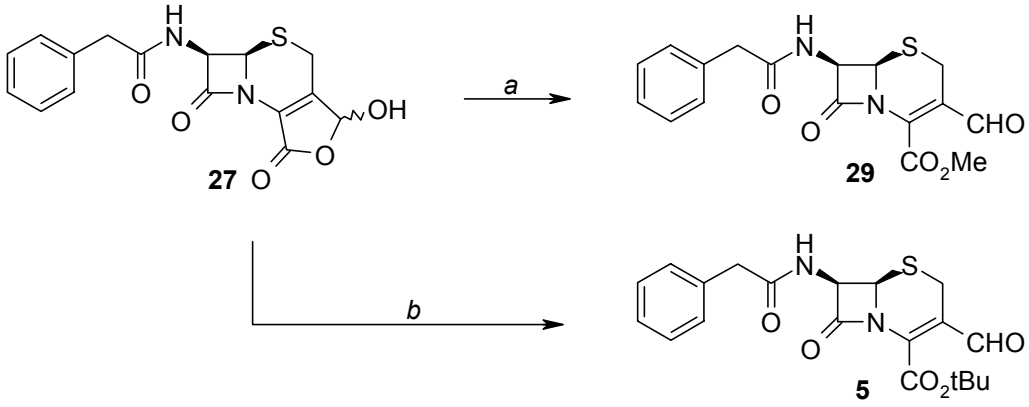
Bromination of lactone **3** was performed according to the method of Sugawara *et al*.[10] Then, simply stirring of the resulting mixture of bromines **26a** and **26b** in a THF/water mixture,[32] resulted in the formation of hydroxylactone **27** in 95% yield, which, actually is in equilibrium with its open aldehyde form **28** (Scheme 9).



a) HCl (conc.), H_2O, acetone, r.t., 15h, 89%; b) Me_3SiCl, Et_3N, DMF, 0°C - r.t., 15h; c) Br_2, 0°C - r.t., 15h, 55%; d) THF / H_2O = (9:1), r.t., 15h and 55°C, 6h, 95%.

Scheme 9.

Treatment of **27** with diazomethane in THF, using the procedure of Sugawara *et al.*,[10] gave methyl ester **29** in 97% (Scheme 10). This product was not subjected to purification by column chromatography on silica gel, because under the relatively acidic conditions at the column, reformation of hydroxylacton **27** may readily occur (similarly as in Scheme 5).



a) CH_2N_2, THF, Et_2O, 0°C, 10', 97%; b) isourea (DCC, tert-BuOH), CH_2Cl_2, r.t., 15h, trace.

Scheme 10.

In order to prevent such a lactonization, the conversion into a *tert*-butyl ester, which is much more stable toward hydroxylacton formation, would be required. Disappointingly, after reaction of the hydroxylacton **27** with the isourea (derived of *tert*-butyl alcohol and DCC), *tert*-butyl ester **5** was formed in only a trace amount.

Therefore, no further attention was paid to this lactone approach. Moreover, at that time it was found that the 7-ACA route appeared to be superior in yield and efficiency when compared with the lactone route.

3.3 Concluding remarks

In conclusion, starting from readily available 7-ACA (**2**), a convenient, high yielding procedure for some 3-formylcephalosporins, *viz*. 3-formylceph-2-em **4** and 3-formylceph-3-em sulfide **5** and the corresponding sulfoxide **6** has been developed. These 3-formyl derivatives are valuable compounds for further synthetic elaboration. Although 7-phenylacetyl-ADCA (**1**) and cephalolactone (**3**) are suitable as starting material, the overall synthetic efficiency of the routes to 3-formylcephalosporins starting from these two compounds is inferior to that using 7-ACA (**2**). The higher oxidation state of the C_{10}-substitution in 7-ACA as compared with 7-ADCA (**1**) turned out to be the decisive factor in its applicability in the synthesis of 3-formylcephalosporins.

3.4 Experimental part

General remarks

100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer and 300 MHz ^{1}H-NMR spectra and all ^{13}C-NMR spectra were recorded on a Bruker AC 300 using Me_4Si as internal standard. All coupling constants are given as ^{3}J in Hz, unless indicated otherwise. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FTS-25 instrument. For mass spectra a double focusing VG7070E mass spectrometer was used. For some samples, High Resolution FAB was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer (JEOL Ltd. 1-2 Musashino 3-chome, Akishima Tokyo), coupled to a MS-MP 9021D/UPD data system (University of Amsterdam). Elemental analyses were conducted on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. For the determination of optical rotations a Perkin-Elmer 241 polarimeter was used. Solvents were dried using the following methods: dichloromethane was distilled from P_2O_5; ethyl acetate was distilled from K_2CO_3; diethyl ether was distilled from NaH; hexane and heptane were distilled from CaH_2; tetrahydrofuran was distilled from sodium just before use. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on a Merck precoated silicagel 60 F254 plates (0.25 mm). Spots were visualized with UV or using a molybdate spray. Flash chromatography was carried out at a pressure of *ca*. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was performed with ACROS silicagel (0.035-0.070 mm; pore diameter ca. 6 nm).

Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada). Bromide **7** was obtained from DSM Anti-Infectives (Delft, The Netherlands).

_N_1-[(5a_R_,6_R_)-1,7-dioxo-1,4,6,7-tetrahydro-3_H_,5a_H_-azeto[2,1-_b_]furo[3,4-_d_][1,3]thiazin-6-yl]-2-phenylacetamide (3)

Following the procedure by Kukolja *et al.*,[30] phenylacetyl-7ACA **13** (0.78 g; 2.0 mmol) was dissolved in a mixture of concentrated hydrochloric acid (4 ml), acetone (16 ml), and water (12 ml). After stirring for 15h at r.t., dichloromethane and saturated $NaHCO_3$ solution were added. Extraction with dichloromethane (2x50 ml) and drying ($MgSO_4$) afforded lactone **3** (0.59 g; 89%) as an off-white solid.
Mp 208-210°C (dec.); $[\alpha]_D$ = +170° (c = 1.0; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$ and few drops DMSO-d_6) δ (ppm) = 3.58 and 3.65 (qAB, J_{AB} = 14.0 Hz, 2H, $PhCH_2$), 3.77 and 3.85 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 5.03 (s, 2H, OCH_2C=), 5.12 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.91 (dd, *J* = 5.0 Hz *J* = 8.5 Hz, 1H, NHC*H*CHS), 7.23-7.37 (m, 5H, PhH), 8.92 (d, *J* = 8.5 Hz, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$ and few drops DMSO-d_6) δ (ppm) = 23.1 (SCH_2), 42.5 ($PhCH_2$), 58.3 (CHNH), 60.7 (CHS), 71.8 (CH_2O), 124.2 (=*C*CH_2O), 127.1, 128.8, 129.8, and 136.6 (PhC), 142.3 (=*C*CO_2CH_2), 165.0 (C=O, lactam), 167.0 (*C*O_2CH_2), 171.7 ($PhCH_2$*C*(O)); IR (KBr): ν 3289 (broad, NH), 1790 (two peaks) (C=O, lactam and lactone), 1652 and 1520 (C=O, amide), 1418 (C-N), 1147 (C-O, lactone) cm^{-1}; MS (CI$^+$): *m/z* (%) = 331 (2) $[M+H]^+$, 298 (16), 156 (15), 118 (19), 112 (50), 91 (100), $[C_7H_7]^+$; elem. anal.: calc. (found) for $C_{16}H_{14}O_4N_2S$: C: 58.17 (58.14), H: 4.27 (4.27), N: 8.48 (8.33).

***tert*-Butyl (4_S_,7_R_,7a_R_)-3-formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4_H_,6_H_-azeto[2,1-_b_][1,3]thiazine-4-carboxylate (4)**

To a stirred solution of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (1.4 g; 5.0 mmol) in DMSO (8 ml) was added a solution of alcohol **16** (1.0 g; 2.48 mmol) in THF (3.0 ml) over a period of 3h. The reaction mixture was stirred for an additional 30h at rt. Then the reaction mixture was extracted with ethyl acetate, the extracts washed with water (3x75 ml), brine (1x75 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, ethyl acetate / hexane 3:7) to furnish aldehyde **4** (0.81 g; 81%) as a white solid.
Mp 146-148°C (dec.); $[\alpha]_D$ = +679° (c = 0.30; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.44 (s, 9H, $C(CH_3)_3$), 3.65 (s, 2H, $PhCH_2$), 5.27 (s, 1H, C*H*$CO_2{}^t$Bu), 5.30 (d, *J* = 3.9 Hz, 1H, NHCHC*H*S), 5.55 (dd, *J* = 3.9 Hz *J* = 7.6 Hz, 1H, NHC*H*CHS), 6.22 (d, *J* = 7.6 Hz, 1H, NH), 7.26-7.40 (m, 5H, PhH), 7.43 (s, 1H, SCH), 9.25 (s, 1H, CHO); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 49.8 (*C*H$CO_2{}^t$Bu) 53.9 (CHNH), 60.4 (CHS), 83.7 (*C*$(CH_3)_3$), 116.1 (=*C*CO_2H), 127.7, 129.1, 129.4 and 133.5 (PhC), 138.0 (SCH) 163.9 (C=O, lactam), 165.7 (CH*C*$O_2{}^t$Bu), 167.5 (*C*O_2H), 171.5 ($PhCH_2$*C*(O)); IR (KBr): ν 3265 (broad, NH), 1768 (C=O, lactam), 1733 (C=O, ester), 1667 and 1544 (C=O, amide), 1369 (C-N), 1152 (O-C, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 425 (30) $[M+Na]^+$, 403 (11) $[M+H]^+$, 347 $[M+H–C_4H_8]^+$, 178 (100); elem. anal.: calc. (found) for $C_{20}H_{22}O_5N_2S$: C: 59.69 (59.73), H: 5.51 (5.59), N: 6.96 (6.93), S: 7.97 (7.97).

***tert*-Butyl (7_R_,7a_R_)-3-formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2_H_,6_H_-azeto[2,1-_b_][1,3]thiazine-4-carboxylate (5)**

This compound was prepared from alcohol **19** (0.566 g; 1.4 mmol) in the same way as described for the synthesis of 3-formylceph-2-em **4** (0.552 g, 96%). An analytical sample (white crystals) was

obtained by column chromatography (SiO_2, ethyl acetate / heptane 1:1) followed by re-crystallization (diethyl ether).

Mp 146-148°C (dec.); $[\alpha]_D$ = +152° (c = 0.51; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.56 (s, 9H, $C(CH_3)_3$), 3.24 and 3.94 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 3.63 and 3.67 (qAB, J_{AB} = 16.0 Hz, 2H, $PhCH_2$), 4.99 (d, *J* = 5.4 Hz, 1H, NHCHC*H*S), 5.95 (dd, *J* = 5.4 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.33 (d, *J* = 9.2 Hz, 1H, NH), 7.25-7.40 (m, 5H, PhH), 9.80 (s, 1H, CHO); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.1 (SCH_2), 27.7 ($C(CH_3)_3$), 43.2 ($PhCH_2$), 58.9 (CHNH), 59.8 (CHS), 85.8 ($C(CH_3)_3$), 122.4 (=*C*CHO), 127.7, 129.2, 129.3 and 133.5 (PhC), 140.2 (=*C*CO_2^{t}Bu), 159.0 (*C*O_2^{t}Bu), 164.7 (C=O, lactam), 171.1 ($PhCH_2$*C*(O)), 187.9 (-CHO); IR (KBr): ν 3334 (broad, NH), 1795 (C=O, lactam), 1705 (C=O, ester), 1668 and 1518 (C=O, amide), 1373 (C-N), 1226 and 1161 (C-O, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 425 (18) $[M+Na]^+$, 403 (13) $[M+H]^+$, 347 (28) $[M+H-C_4H_8]^+$, 176 (100); elem. anal.: calc. (found) for $C_{20}H_{22}O_5N_2S$: C: 59.69 (59.51), H: 5.51 (5.53), N: 6.96 (6.88), S: 7.97 (7.94).

tert-Butyl (7*R*,7a*R*)-3-formyl-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (6)

This compound was prepared from alcohol **9** (0.421 g; 1.0 mmol) in the same way as described for the synthesis of 3-formylceph-2-em **4**. Purification by chromatography (SiO_2, ethyl acetate / heptane 2:1) afforded **6** as a white solid (0.398 g; 95%).

Mp 175-176°C (dec.); $[\alpha]_D$ = -153° (c = 0.48; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.58 (s, 9H, $C(CH_3)_3$), 2.85 (dd, *J* = 18.4 Hz ^{4}*J* = 1.6 Hz, 1H, SCH_2), 3.63 (s, 2H, $PhCH_2$), 4.40 (d, *J* = 18.4 Hz, 1H, SCH_2), 4.47 (dd, *J* = 5.2 Hz ^{4}*J* = 1.6 Hz, 1H, NHCHC*H*S), 6.16 (dd, *J* = 5.2 Hz *J* = 9.9 Hz, 1H, NHC*H*CHS), 6.91 (d, *J* = 9.9 Hz, 1H, NH), 7.25-7.37 (m, 5H, PhH), 9.97 (s, 1H, CHO); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.7 ($C(CH_3)_3$), 41.4 (SCH_2), 43.1 ($PhCH_2$), 60.0 (CHNH), 67.6 (CHS), 86.3 ($C(CH_3)_3$), 116.5 (=*C*CHO), 127.6, 129.0, 129.3 and 133.6 (PhC), 139.9 (=*C*CO_2^{t}Bu), 158.2 (*C*O_2^{t}Bu), 164.5 (C=O, lactam), 171.3 ($PhCH_2$*C*(O)), 188.4 (CHO); IR (KBr): ν 3324 (broad, NH), 1800 (C=O, lactam), 1705 (C=O, ester), 1672 and 1520 (C=O, amide), 1370 (C-N), 1153 (C-O, ester), 1025 (S=O) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 441 (2) $[M+Na]^+$, 419 (2) $[M+H]^+$, 363 (80) $[M+H-C_4H_8]^+$, 91 (100) $[PhCH_2^+]$; HRMS (FAB, m/z): calculated for $C_{20}H_{22}O_6N_2SNa^+$: 441.1096 amu. Found: 441.1059 ± 0.0044 amu.

tert-Butyl (7*R*,7a*R*)-3-(iodomethyl)-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (8)

To a stirred solution of bromide **7** (1.0 g; 2.22 mmol) in dry acetone (25 ml), sodium iodide (0.665g; 4.44 mmol) was added in one portion. The suspension was stirred in the dark at r.t. for 5h and then for 2.5h at 45°C. The color of the reaction mixture turned light brown. Acetone was removed *in vacuo*, ethyl acetate (75 ml) and 10% sodium thiosulfate ($Na_2S_2O_3$) were added, and the clear aqueous solution was extracted with ethyl acetate (2x75 ml). The combined organic layers were washed with saturated $NaHCO_3$ (1x75 ml) and brine (1x75 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The pale yellow solid **8** (1.07 g; 97%) was used without further purification.

Mp 153-155°C (dec.); $[\alpha]_D$ = -36.8° (c = 1.04; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.55 (s, 9H, $C(CH_3)_3$), 3.44 and 3.69 (qAB, J_{AB} = 18.2 Hz, 2H, SCH_2), 3.60 (s, 2H, $PhCH_2$), 4.23 and 4.58 (qAB, J_{AB} = 9.6 Hz, 2H, CH_2I), 4.46 (dd, *J* = 4.8 Hz ^{4}*J* < 1.5 Hz, 1H, NHCHC*H*S), 5.97 (dd, *J* = 4.8 Hz *J* = 9.8 Hz, 1H, NHC*H*CHS), 6.95 (d, *J* = 9.8 Hz, 1H, NH), 7.25-7.37 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 4.7 (CH_2I), 27.8 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 47.5 (SCH_2), 58.9 (CHNH), 67.1 (CHS), 84.4 ($C(CH_3)_3$), 121.3 (=*C*CH_2I), 124.7 (=*C*CO_2^{t}Bu) 127.4, 128.9, 129.3 and 133.8 (PhC), 159.5 (=C*C*O_2^{t}Bu),

163.6 (C=O, lactam), 171.4 ($PhCH_2C(O)$); IR (KBr): ν 3261 (broad, NH), 1785 (C=O, lactam), 1713 (C=O, ester), 1677 and 1522 (C=O, amide), 1369 (C-N), 1150 (C-O, ester), 1029 (S=O) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 553 (4) $[M+Na]^+$, 531 (11) $[M+H]^+$, 475 (30) $[M+H-C_4H_8]^+$, 403 (24) $[M-I]^+$, 347 (40) $[M+H-I-C_4H_8]^+$, 154 (100) $[NOBA]^*$, 91 (80) $[PhCH_2^+]$, 57 (60) $[C_4H_9^+]$ (* defragmentation of NOBA matrix); HRMS (FAB, m/z): calculated for $C_{20}H_{24}O_5N_2SI^+$: 531.0451 amu. Found: 531.0421 ± 0.0053 amu.

***tert*-Butyl (7*R*,7a*R*)-3-(hydroxymethyl)-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ⁴-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (9)**

The procedure as described for the preparation of the sulfide analogue was followed using phenylacetyl protected 7-ACA-sulfoxide **21** (1.5 g; 3.7 mmol), immobilized cephalosporin acetyl hydrolase (4 g "wet" enzyme) and isourea (4 equiv.) derived from *tert*-butyl alcohol and DCC. Work-up after 4-6h, followed by purification *via* chromatography (SiO_2, ethyl acetate) afforded *tert*-butyl ester **9** as a white solid (0.96 g; 62%). An analytical sample was obtained by crystallization from ethyl acetate and heptane affording colorless plates.

Alternative approach

Alcohol **16** (1.0 g; 2.48 mmol) was oxidized with *m*-CPBA (0.57 g; 2.5 mmol) in dichloromethane (50 ml) at 0°C for 2h. After addition of aqueous $NaHCO_3$ the mixture was extracted with dichloromethane (2x50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* giving sulfoxide **9** (0.83 g; 80%) as a white solid.

Mp 198-199°C (dec.); $[\alpha]_D$ = +87° (c = 0.51; acetone); ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) = 1.49 (s, 9H, $C(CH_3)_3$), 3.53 and 3.85 (qAB, J_{AB} = 18.6 Hz, 2H, SCH_2), 3.49 and 3.75 (qAB, J_{AB} = 14.1 Hz, 2H, $PhCH_2$), 4.07 and 4.42 (dqAB, J_{AB} = 13.9 Hz *J* = 5.6 Hz, 2H, C*H*$_2$OH), 4.83 (d, *J* = 4.5 Hz, 1H, NHCHC*H*S), 5.13 (t, *J* = 5.6 Hz, 1H, CH_2OH) 5.87 (dd, *J* = 4.5 Hz *J* = 8.4 Hz, 1H, NHC*H*CHS), 7.23-7.31 (m, 5H, PhH), 8.34 (d, *J* = 8.4 Hz, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm) = 27.7 ($C(CH_3)_3$), 41.7 (SCH_2), 45.5 ($PhCH_2$), 58.2 (CH_2OH), 60.4 (CHNH), 66.4 (CHS), 82.6 ($C(CH_3)_3$), 123.3 (=CCO_2^{t}Bu), 125.7 (=CCH_2OH), 126.7, 128.5, 129.3 and 136.4 (PhC), 160.2 (CO_2^{t}Bu), 164.2 (C=O, lactam), 171.2 ($PhCH_2C(O)$); IR (KBr): ν 3509 (broad, OH), 3229 (broad, NH), 1782 (C=O, lactam), 1695 (C=O, ester), 1661 and 1541 (C=O, amide), 1327 (C-N), 1159 (C-O, ester), 1031 (S=O) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 443 (18) $[M+Na]^+$, 421 (5) $[M+H]^+$, 403 (10), 387 (10), 365 (12), 347 (38), 225 (48), 91 (92) $[PhCH_2^+]$, 57 (100) $[C_4H_9^+]$; elem. anal.: calc. (found) for $C_{20}H_{24}O_6N_2S$: C: 57.13 (56.73), H: 5.75 (5.71), N: 6.66 (6.62).

***tert*-Butyl (7*R*,7a*R*)-3-[(acetyloxy)methyl]-6-oxo-7-(tritylamino)-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (10)**

In a sealable flask (Grolsch beer bottle) 7-ACA (**2**) (10.0 g; 36.7 mmol) was suspended in dimethoxyethane (100 ml). After cooling below -10°C, concentrated sulfuric acid (9.3 ml) and isobutene (100 ml) were added and the flask was closed. The mixture was stirred for 3 days at r.t.. After cooling below -10°C, the flask was opened and the reaction mixture was quenched with a saturated solution of $NaHCO_3$ at 0°C. The aqueous layer was extracted with ethyl acetate (2x100 ml), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude *tert*-butyl ester was dissolved in dichloromethane under nitrogen, followed by addition of triethyl amine (3.8 ml; 55 mmol) and trityl chloride (5.6 g; 40.4 mmol). The mixture was stirred for 15h at r.t.. Then, water was added and the mixture was extracted with ethyl acetate (2x100 ml). The combined organic layers were washed with an aqueous NH_4Cl solution, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was

purified by flash chromatography (SiO_2, ethyl acetate / hexane 1:6) to give **10** (2.6 g; 13%) as an off-white solid with the double bond at the Δ^2-position.

Mp 81-83°C (dec.); $[\alpha]_D$ = +338° (c = 1.04; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.40 (s, 9H, $C(CH_3)_3$), 2.05 (s, 3H, $C(O)CH_3$), 3.14 (s, 1H, NH), 4.35 (d, *J* = 3.7 Hz, 1H, NHCHC*H*S), 4.45 and 4.66 (qAB, J_{AB} = 12.6 Hz, 2H, CH_2OAc), 4.67 (dd, *J* = 3.7 Hz *J* = 11.7 Hz, 1H, NHC*H*CHS), 4.87 (s, 1H, C*H*$CO_2{}^t$Bu), 6.20 (s, 1H, SCH=), 7.24-7.54 (m, 15H, TritylH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 20.8 (OC(O)*C*H_3), 27.8 (C(*C*H_3)$_3$), 50.3 (*C*H$CO_2{}^t$Bu) 56.2 (CHS), 65.4 (CH_2OAc), 67.7 (CHNH), 70.5 (*C*Ph_3), 83.4 (*C*$(CH_3)_3$), 118.6 (SCH=), 127.8 (=*C*CH_2OAc), 122.4, 126.8, 128.2, 128.4 and 145.1 (tritylC), 166.5 (C=O, lactam), 168.6 (CH*C*$O_2{}^t$Bu), 170.5 (O*C*(O)CH_3); IR (KBr): ν 3250 (broad, NH), 3056 and 2975 and 2934 (=CH, trityl), 1774 (C=O, lactam), 1744 (C=O, ester and acetyl), 1370 (C-N), 1148 (C-O, ester) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 570 (14) [M^+], 327 (3) [M+H-Ph_3C]$^+$, 243 (100) [Ph_3C^+], 165 (10), 57 (4) [$C_4H_9^+$]; HRMS (FAB, m/z): calculated for $C_{33}H_{35}O_5N_2S^+$: 571.2267 amu. Found: 571.2267 ± 0.0057 amu.

***tert*-Butyl (7*R*,7a*R*)-3-(iodomethyl)-6-oxo-7-(tritylamino)-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (11)**

The transformation of the acetate into the iodide was accomplished in a similar manner, as described by Mobashery *et al*..[15] To a solution of protected 7-ACA **10** (1.0 g; 1.75 mmol) in dichloromethane (10 ml) under nitrogen, trimethylsilyl iodide (1.5 equiv.; ca. 0.4 ml) was slowly added. The organic layer was extracted successively with 10% NaS_2O_3 solution, water, saturated $NaHCO_3$ solution and water, dried ($MgSO_4$) and concentrated *in vacuo* to ca. 5 ml. The product was precipitated by addition of hexane (50 ml) and isolated by filtration as a yellow solid **11** (0.80 g; 72%).

Mp 84-86°C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.42 (s, 9H, $C(CH_3)_3$), 3.15 (bs, 1H, NH), 4.97 and 4.22 (qAB, J_{AB} = 10.0 Hz, 2H, CH_2I), 4.31 (d, *J* = 3.7 Hz, 1H, NHCHC*H*S), 4.67 (bd, *J* = 2.9 Hz, 1H, NHC*H*CHS), 5.15 (s, 1H, C*H*$CO_2{}^t$Bu), 6.30 (s, 1H, SCH=), 7.24-7.54 (m, 15H, TritylH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 8.4 (CH_2I), 27.9 (C(*C*H_3)$_3$), 50.7 (*C*H$CO_2{}^t$Bu) 56.2 (CHS), 67.9 (CHNH), 70.6 (*C*Ph_3), 83.7 (*C*$(CH_3)_3$), 121.0 (SCH=), 121.3 (=*C*CH_2I), 126.8, 128.2, 128.4 and 145.1 (TritylC), 166.6 (C=O, lactam), 168.3 (CH*C*$O_2{}^t$Bu); IR (KBr): ν 3320 (broad, NH), 3056 and 2973 and 2927 (=CH, trityl), 1776 (C=O, lactam), 1736 (C=O, ester), 1370 (C-N), 1148 (C-O, ester) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 638 (5) [M^+], 395 (1) [M+H-Ph_3C]$^+$, 243 (100) [Ph_3C^+], 154 (14), 57 (5) [$C_4H_9^+$]; HRMS (FAB, m/z): calculated for $C_{33}H_{35}O_5N_2S^+$: 638.1100 amu. Found: 638.1144 ± 0.0064 amu.

***tert*-Butyl (7*R*,7a*R*)-3-formyl-6-oxo-7-(tritylamino)-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (12)**

Oxidation of compound **11** was accomplished by vigorously stirring a mixture of iodomethyl **11** (0.100 g; 0.157 mmol), vanadyl sulfate (200 wt% $VOSO_4.5H_2O$; 0.200 g) under an oxygen atmosphere for 2h as was previously described by Tanaka *et al*..[9] Work-up was performed by filtration to remove all solids. The filtrate was diluted with ethyl acetate and washed with aqueous NaS_2O_3 and brine, dried over $MgSO_4$, and concentrated *in vacuo*. TLC analysis (ethyl acetate / hexane = 1:3) of the crude product showed several spots, but ^{1}H-NMR ($CDCl_3$) showed formation of an aldehyde (singlet at 9.10 ppm). Due to the complexity of the crude mixture of products, no attempt to purification were made.

(7*R*,7a*R*)-3-[(Acetyloxy)methyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylic acid (13)

To a solution of 7-ACA (**2**) (12.0 g; 44.1 mmol) in saturated aqueous $NaHCO_3$ (300 ml) and acetone (100 ml) was added phenylacetyl chloride (*ca.* 2 equiv.; *ca.* 6 ml) in two portions. After 17h of stirring, the reaction mixture was acidified with concentrated HCl to pH 1.5 and extracted with dichloromethane (2x250 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was suspended in diethyl ether and stirred for 17h to remove phenylacetic acid (by-product). The product was filtered off, washed with diethyl ether and dried *in vacuo*. Phenylacetyl protected 7-ACA **13** was obtained as an off-white solid (14.2 g; 83%) and was used without further purification.

Mp 168-171°C (dec.); $[\alpha]_D$ = +86° (c = 1.0; dioxane); ^{1}H-NMR (100 MHz, $CDCl_3$ and DMSO-d_6) δ (ppm) = 2.07 (s, 3H, CH_3), 3.32 and 3.54 (qAB, J_{AB} = 15.0 Hz, 2H, SCH_2), 3.58 (s, 2H, $PhCH_2$), 4.84 and 5.08 (qAB, J_{AB} = 13.3 Hz, 2H, C*H*$_2$OAc), 4.95 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 5.77 (dd, *J* = 4.8 Hz *J* = 8.5 Hz, 1H, NHC*H*CHS), 7.29 (m, 5H, PhH), 8.18 (d, *J* = 8.5 Hz, 1H, NH), 9.64 (s, 1H, CO_2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm) = 20.8 (OC(O)*C*H$_3$), 25.7 (SCH_2), 41.8 ($PhCH_2$), 57.6 (CHNH), 59.3 (CHS), 62.9 (CH_2OAc), 123.6 (=*C*CH$_2$OAc) 126.5 (=*C*CO$_2$H), 126.7, 128.4, 129.2 and 136.0 (PhC), 163.0 (C=O, lactam), 165.0 (CO_2H), 170.4 (O*C*(O)CH$_3$), 171.2 (PhCH$_2$*C*(O)); IR (KBr): ν 3260 (broad, NH), 1782 (C=O, lactam), 1748 (C=O, acetyl), 1738 (C=O, acid), 1658 and 1535 (C=O, amide), 1345 (C-N), 1228 (C-O, acetyl) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 413 (50) $[M+Na]^+$, 391 (17) $[M+H]^+$, 331 (100) $[M+H-CO_2CH_3]^+$ 156 (85), 94 (67).

***tert*-Butyl (4*S*,7*R*,7a*R*)-3-[(acetyloxy)methyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (15)**

DCC (5.81 g; 28.2 mmol) was added to a cooled (-30°C) and stirred suspension of phenylacetyl protected 7-ACA **13** (10 g; 25.6 mmol), *tert*-butyl alcohol (5 ml) and DMAP (200 mg) in dichloromethane (200 ml) under nitrogen. The reaction mixture was stirred for 1h at 0°C and for another 15h at r.t.. After removal of DCU by filtration, 2N HCl was added to the filtrate. Crude *tert*-butyl ester was obtained by extraction with dichloromethane (3x150 ml), washing with saturated $NaHCO_3$ (1x75 ml) and brine (1x75 ml), drying ($MgSO_4$) and concentration *in vacuo*. Recrystallization from ethyl acetate / heptane after treatment with active carbon gave pure *tert*-butyl ester **15** as white needles (10.1 g; 88%).

Mp 227-229°C; $[\alpha]_D$ = +409° (c = 0.53; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.47 (s, 9H, C(CH$_3$)$_3$), 2.06 (s, 3H, C(O)CH$_3$), 3.64 (s, 2H, $PhCH_2$), 4.53 and 4.71 (qAB, J_{AB} = 12.7 Hz, 2H, CH_2OAc), 4.87 (s, 1H, C*H*CO$_2$^{t}Bu), 5.26 (d, *J* = 4.0 Hz, 1H, NHCHC*H*S), 5.65 (dd, *J* = 4.0 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 6.23 (d, *J* = 8.7 Hz, 1H, NH), 6.34 (s, 1H, SCH=), 7.26-7.40 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 20.8 (OC(O)*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 43.3 ($PhCH_2$), 50.6 (*C*HCO$_2$^{t}Bu), 53.4 (CHNH), 60.2 (CHS), 65.4 (CH_2OH), 84.0 (*C*(CH$_3$)$_3$), 119.4 (SCH=), 121.2 (=*C*CH$_2$OAc), 127.6, 129.1, 129.4 and 133.6 (PhC), 164.2 (C=O, lactam), 165.9 (CH*C*O$_2$^{t}Bu), 170.4 (O*C*(O)CH$_3$), 171.0 (PhCH$_2$*C*(O)); IR (KBr): ν 3246 (broad, NH), 3058 (CH, phenyl), 1782 (C=O, lactam), 1736 (C=O, ester and acetyl), 1649 and 1560 (C=O, amide), 1387 (C-N), 1218 (C-O, acetyl) 1153 (C-O, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 446 (5) $[M^+]$, 405 (3) $[M+H-COCH_3]^+$, 345 (14) $[M+H-COCH_3-C_4H_8]^+$, 331 (60), 176 (72), 216 (95), 91 (100) $[C_7H_7^+]$; HRMS (EI, m/z): calculated for $C_{22}H_{26}O_6N_2S$: 446.15115 amu. Found: 446.15036 ± 0.00134 amu.

***tert*-Butyl (4*S*,7*R*,7a*R*)-3-(hydroxymethyl)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (16)**

Sodium hydroxide (0.90 g; 22.4 mmol) in methanol (30 ml) was added under nitrogen to a cooled (-30°C) and stirred solution of triple protected 7-ACA **15** (5.0 g; 0.011 mol) in methanol (360 ml). The reaction mixture was stirred between -30 and -20°C for 4-5h until TLC analysis (ethyl acetate / hexane 1:1) showed completion of the reaction. The reaction mixture was then poured into diluted HCl solution and extracted with CH_2Cl_2 (3x100 ml). The combined organic layers were washed with brine (1x50 ml), water (1x50 ml), dried ($MgSO_4$) and concentrated *in vacuo* affording crude alcohol **16** as a yellow-orange foam (4.44 g; 98%). An analytical sample (white solid) was obtained after column chromatography (SiO_2, ethyl acetate / heptane 2:1).

Mp 85-87°C (dec.); $[\alpha]_D$ = +471° (c = 0.525; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.48 (s, 9H, $C(CH_3)_3$), 2.46 (bs, 1H, CH_2OH), 3.63 (s, 2H, $PhCH_2$), 4.12 and 4.21 (dqAB, J_{AB} = 13.4 Hz J = 5.5 Hz, 2H, CH_2OH), 4.92 (d, ^4J = ~1.0 Hz, 1H, $CHCO_2{}^tBu$), 5.22 (d, J = 4.0 Hz, 1H, NHCHCHS), 5.61 (dd, J = 4.0 Hz J = 8.7 Hz, 1H, NHCHCHS), 6.23 (d, ^4J = ~1.0 Hz, 1H, SCH), 6.27 (bs, 1H, NH), 7.26-7.38 (m, 5H, PhH), ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.9 ($C(CH_3)_3$), 43.2 ($PhCH_2$), 50.7 ($CHCO_2{}^tBu$) 53.6 (CHNH), 60.1 (CHS), 64.9 (CH_2OH), 84.0 ($C(CH_3)_3$), 117.2 (SCH=), 124.3 (=CCH_2OH) 127.6, 129.0, 129.4 and 133.8 (PhC), 164.5 (C=O lactam), 166.5 ($CHCO_2{}^tBu$), 171.2 ($PhCH_2C(O)$); IR (KBr): ν 3431 (broad, OH), 3298 (broad, NH), 1770 (C=O, lactam), 1732 (C=O, ester), 1660 and 1535 (C=O, amide), 1369 (C-N), 1151 (O-C, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 427 (21) [M+Na]$^+$, 404 (5) [M$^+$], 331 (35) [M+H–C_4H_8–H_2O]$^+$, 176 (57), 57 (100) [$C_4H_4^+$]; elem. anal.: calc. (found) for $C_{20}H_{24}O_5N_2S$: C: 59.39 (59.39), H: 5.98 (5.97), N: 6.93 (6.83), S: 7.93 (8.07).

***tert*-Butyl (7*R*,7a*R*)-3-[(acetyloxy)methyl]-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (17)**

This reaction was carried out in a similar manner as described by Murphy *et al*..[31] A solution of Δ^2-ester **15** (2.6 g; 5.8 mmol) in chloroform (100 ml) was added to a solution of *meta*-chloroperbenzoic acid (1.1 equiv.; 1.57 g) in chloroform (15 ml) at 0°C. After stirring for 2h, TLC analysis showed completion of the reaction. The organic layer was washed with saturated $NaHCO_3$ (1x75 ml) and brine (1x75 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Then methanol was added and the resulting solution was concentrated *in vacuo* again. Sulfoxide **17** was obtained as a jelly compound (2.65 g; 98%). An analytical sample (white crystals) was obtained by recrystallization from diethyl ether.

Mp 144-146°C (dec.); $[\alpha]_D$ = +56.2° (c = 0.99; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.53 (s, 9H, $C(CH_3)_3$), 2.07 (s, 3H, $C(O)CH_3$), 3.18 and 3.72 (qAB, J_{AB} = 18.6 Hz, 2H, SCH_2), 3.61 (s, 2H, $PhCH_2$), 4.43 (d, J = 4.7 Hz, 1H, NHCHCHS), 4.67 and 5.29 (qAB, J_{AB} = 13.6 Hz, 2H, CH_2OAc), 6.02 (dd, J = 4.7 Hz J = 9.7 Hz, 1H, NHCHCHS), 6.90 (d, J = 9.7 Hz, 1H, NH), 7.26-7.33 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 20.7 ($OC(O)CH_3$), 27.7 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 45.7 (SCH_2), 59.0 (CHNH), 63.2 (CH_2OAc), 66.7 (CHS), 84.3 ($C(CH_3)_3$), 118.0 (=CCH_2OAc), 127.0 (=$CCO_2{}^tBu$) 127.4, 128.9, 129.3 and 133.8 (PhC), 159.2 (=$CCO_2{}^tBu$), 164.0 (C=O, lactam), 170.4 ($OC(O)CH_3$), 171.4 ($PhCH_2C(O)$); IR (KBr): ν 3276 (broad, NH), 2978 (CH, phenyl), 1787 (C=O, lactam), 1744 (C=O, acetyl), 1720 (C=O, ester), 1669 and 1527 (C=O, amide), 1380 (C-N), 1226 (C-O, acetyl), 1154 (C-O, ester), 1047 (S=O) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 485 (18) [M+Na]$^+$, 463 (14) [M+H]$^+$, 407 (25) [M-C_4H_8]$^+$, 403 (47) [M-AcOH]$^+$, 347 (100) [M+H-AcOH-C_4H_8]$^+$, 91 (34) [$PhCH_2^+$]; HRMS (FAB, m/z): calculated for $C_{22}H_{27}O_7N_2S^+$: 463.1539 amu. Found: 463.1546 ± 0.0046 amu.

***tert*-Butyl (7*R*,7a*R*)-3-[(acetyloxy)methyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (18)**

A slurry of dicylcohexylcarbodiimide (30.4 g; 0.147 mol), *tert*-butyl alcohol (12.8 g; 0.173 mol), and copper(I) chloride (0.3 g; catalyst) was stirred for 3 days. After filtration, 9 ml were diluted with dichloromethane (12 ml) and this mixture was added to 7-phenylacetyl-ACA **13** (3.9 g; 10 mmol) in dichloromethane (30 ml) at r.t.. After 15h, 2N HCl (40 ml) was added to the reaction mixture and the dicyclohexyl urea was removed by filtration. The organic layer was washed with saturated $NaHCO_3$ and water successively, dried ($MgSO_4$), treated with active carbon and concentrated to a small volume. Then toluene was added and the mixture was stored at 4°C overnight. The purified (off-white) *tert*-butyl ester **18** (3.54 g; 79%) was isolated by filtration.

Mp 159-161°C; $[\alpha]_D$ = +65.1° (c = 1.0; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.51 (s, 9H, $C(CH_3)_3$), 2.07 (s, 3H, $C(O)CH_3$), 3.31 and 3.50 (qAB, J_{AB} = 18.4 Hz, 2H, SCH_2), 3.64 (s, 2H, $PhCH_2$), 4.77 and 5.05 (qAB, J_{AB} = 13.2 Hz, 2H, CH_2OAc), 4.92 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 5.82 (dd, *J* = 4.9 Hz *J* = 9.1 Hz, 1H, NHC*H*CHS), 6.28 (d, *J* = 9.1 Hz, 1H, NH), 7.26-7.31 (m, 5H, PhH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 20.6 ($OC(O)CH_3$), 27.7 ($C(CH_3)_3$), 43.2 ($PhCH_2$), 49.1 (SCH_2), 57.3 (CHNH), 59.2 (CHS), 63.0 (CH_2OAc), 83.8 ($C(CH_3)_3$), 123.5 (=CCH_2OAc), 127.3 (=C$CO_2{}^tBu$) 127.6, 129.1, 129.4 and 133.8 (PhC), 160.2 (=C$CO_2{}^tBu$), 164.3 (C=O, lactam), 170.5 (O*C*(O)CH_3), 171.2 ($PhCH_2C(O)$); IR (KBr): ν 3287 (broad, NH), 2936 (CH, phenyl), 1790 (C=O, lactam), 1742 (C=O, acetyl), 1715 (C=O, ester), 1657 and 1538 (C=O, amide), 1385 (C-N), 1237 (C-O, acetyl), 1150 (C-O, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 446 (1) [M^+], 387 (8) [M-HOAc]$^+$, 331 (100) [M-HOAc-C_4H_8]$^+$, 176 (51), 91 (53) [$PhCH_2^+$], 57 (43) [$C_4H_9^+$]; HRMS (CI, m/z): calculated for $C_{22}H_{26}O_6N_2S$: 446.15115 amu. Found: 446.15042 ± 0.00133 amu.

***tert*-Butyl (7*R*,7a*R*)-3-(hydroxymethyl)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (19)**

Phenylacetyl protected 7-ACA **13** (4.0 g; 10.2 mmol) was dissolved in water (25 ml) and the pH was set to 7.0 with 0.6 M NaOH. After addition of immobilized cephalosporin acetyl hydrolase (8 g "wet" enzyme) the pH was maintained at pH 7.0 by addition of 0.1 M NaOH (pH stat conditions). After completion of the reaction (4-6h) the enzyme was recovered by filtration. The filtrate was acidified to pH 1.8 after cooling to 0°C. The then formed precipitate was collected by filtration and dried *in vacuo* or extracted (3x75 ml) with ethyl acetate. The combined organic layers were washed with water (2x75 ml) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product **20** was dissolved in dry THF. At room temperature, the carboxylic acid was esterified with isourea derived from *tert*-butyl alcohol and DCC (4 equiv.).[21] After stirring for 17h, DCU was removed by filtration. After addition of 2N HCl, the filtrate was extracted with dichloromethane (3x75 ml). The combined organic layers were extracted with saturated $NaHCO_3$ (1x100 ml) and brine (1x100 ml), dried ($MgSO_4$) providing *tert*-butyl ester **19** after column chromatography (SiO_2, heptane / ethyl acetate 1:2) as a white solid (2.1 g; 61%).

Mp 174-176°C (dec.); $[\alpha]_D$ = +83° (c = 0.87; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.66 (s, 9H, $C(CH_3)_3$), 3.00 (bs, 1H, OH), 3.49 and 3.53 (qAB, J_{AB} = 18.6 Hz, 2H, SCH_2), 3.61 and 3.65 (qAB, J_{AB} = 15.9 Hz, 2H, $PhCH_2$), 3.86 (dd, *J* = 5.0 Hz *J* = 12.6 Hz, 1H, C*H*$_2$OH), 4.46 (d, *J* = 12.6 Hz, 1H, C*H*$_2$OH), 4.89 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 5.83 (dd, *J* = 4.9 Hz *J* = 9.1 Hz, 1H, NHC*H*CHS), 6.53 (d, *J* = 9.1 Hz, 1H, NH), 7.25-7.38 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 25.6 (SCH_2), 27.3 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 57.1 (CH_2OH), 59.0 (CHNH), 61.9 (CHS), 84.0 ($C(CH_3)_3$), 126.5, 127.6, 129.1, 129.4, 129.9, 133.7 (=C$CO_2{}^tBu$, =CCH_2OH and PhC), 161.4 ($CO_2{}^tBu$), 164.6 (C=O, lactam), 171.3

($PhCH_2C(O)$); IR (KBr): ν 3409 (broad, OH), 3298 (broad, NH), 1756 (C=O, lactam), 1709 (C=O, ester), 1661 and 1536 (C=O, amide), 1367 (C-N), 1163 (C-O, ester) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 427 (44) $[M+Na]^+$, 405 (17) $[M+H]^+$, 387 (42) $[M+H–H_2O]^+$, 331 (49) $[M+H–C_4H_8–H_2O]^+$, 178 (100); elem. anal.: calc. (found) for $C_{20}H_{24}O_5N_2S$: C: 59.39 (59.36), H: 5.98 (6.03), N: 6.93 (6.87), S: 7.93 (8.14).

(7*R*,7a*R*)-3-[(Acetyloxy)methyl]-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ⁴-azeto[2,1-*b*][1,3]thiazine-4-carboxylic acid (21)

To a cooled (0°C) suspension of phenylacetyl protected 7-ACA **13** (0.78 g; 2.0 mmol) in dichloromethane (50 ml) 1.5 equiv. of pre-dried *m*-CPBA (0.518 g) was added in one portion while stirring. After additional stirring for 1.5h the precipitate (white solid) was collected by filtration, washed (2x75 ml) with CH_2Cl_2 to remove *m*-CBA, and dried *in vacuo*. The crude sulfoxide **21** (0.80 g; 98%) was used without further purification.

Mp 197-198°C (dec.); $[\alpha]_D$ = +161° (c = 0.87; H_2O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) = 2.02 (s, 3H, CH_3), 3.52 and 3.73 (qAB, J_{AB} = 14.4 Hz, 2H, $PhCH_2$), 3.56 and 3.88 (qAB, J_{AB} = 18.5 Hz, 2H, SCH_2), 4.59 and 5.19 (qAX, J_{AX} = 13.1 Hz, 2H, C*H*$_2$OAc), 4.86 (d, *J* = 4.2 Hz, 1H, NHCHC*H*S), 5.81 (dd, *J* = 4.2 Hz *J* = 8.2 Hz, 1H, NHC*H*CHS), 7.21-7.31 (m, 5H, PhH), 8.40 (d, *J* = 8.2 Hz, 1H, NH); ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm) = 20.8 (OC(O)CH_3), 41.6 ($PhCH_2$), 45.5 (SCH_2), 58.4 (CH_2OAc), 63.2 (CHS), 66.4 (CHS), 118.7 (=CCH_2OAc) 126.1 (=CCO_2H), 126.7, 128.5, 129.3 and 136.0 (PhC), 162.3 (C=O lactam), 164.4 (CO_2H), 170.3 (O*C*(O)CH_3), 171.2 ($PhCH_2C(O)$); IR (KBr): ν 3298 (broad, NH), 1775 (C=O, lactam), 1742 (C=O, acetyl), 1723 (C=O, acid), 1658 and 1527 (C=O, amide), 1339 (C-N), 1222 (C-O, acetyl), 1035 (S=O) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 429 (14) $[M+Na]^+$, 407 (3) $[M+H]^+$, 347 (12) $[M+H\text{-}COCH_3]^+$, 176 (18), ; 154 (100) $[NOBA]^*$, 57 (56) $[C_4H_9^+]$ (* defragmentation of NOBA matrix); HRMS (FAB, m/z): calculated for $C_{18}H_{19}O_7N_2S^+$: 407.0913 amu. Found: 407.0877 ± 0.0041 amu.

(3R) and (3S) *N*1-[(5a*R*,6*R*)-3-bromo-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (26a,b)

Bromination was accomplished by silylation followed by addition of molecular bromine as was previously described by Sugawara *et al*..[10] Bromolactone **26a** and its diastereomer **26b** were obtained as colorless crystals in an overall yield of 55% (literature[10] 78%).

All data were in complete agreement with those reported previously.[10]

***N*1-[(5a*R*,6*R*)-3-hydroxy-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (27)**

A mixture of bromolactones **26a** and **26b** (0.5 g; 1.22 mmol) was dissolved in THF containing 10% water and stirred for 15h at r.t., and then for 6h at 55°C. After removal of the THF under reduced pressure, the product was extracted with dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product **27** (0.40 g; 95%) was dissolved in THF and precipitated by addition of a mixture (1:1) of ethyl acetate and hexane, which gave an analytical sample.

All data were in agreement with those reported previously.[10]

Methyl (7*R*,7a*R*)-3-formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (29)

To a solution of hydroxylactone **27** (600 mg; 1.73 mmol) in dry tetrahydrofuran (5 ml) was added an excess of diazomethane in diethyl ether at 0°C until the reaction mixture was colored brightly yellow.

After 10 min. the reaction was complete and the solution was concentrated to dryness affording aldehyde **29** as a white foam (0.605 g; 97%). Purification by column chromatography (SiO_2, ethyl acetate / hexane 1:1) gave an analytical sample. Probably due to the acidity of the silicagel, also some hydrolysis of the methyl ester had occurred.
^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 3.19 and 3.91 (qAB, J_{AB} = 18.4 Hz, 2H, SCH_2), 3.58 (s, 2H, $PhCH_2$), 3.87 (s, 3H, CO_2Me), 4.95 (d, *J* = 5.3 Hz, 1H, NHCHC*H*S), 5.89 (dd, *J* = 5.3 Hz *J* = 9.1 Hz, 1H, NHC*H*CHS), 6.24 (d, *J* = 9.1 Hz, 1H, NH), 7.20-7.260 (m, 5H, PhH), 9.72 (s, 1H, CHO).

3.5 Crystal structure data

***tert*-Butyl (7*R*,7a*R*)-3-formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (5)**
Crystals of aldehyde **5** suitable for X-ray diffraction studies were obtained from heptane-ethyl acetate. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, θ-2θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[33] was applied. The structure was solved by the program CRUNCH[34] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[35] with anisotropic parameters for the non-hydrogen atoms. All hydrogen atoms were initially placed at calculated positions and were freely refined, subsequently. A structure determination summary, a list of atom coordinates, a list of bond lengths and angles, a list of hydrogen coordinates, and a list of anisotropic displacement parameters are given in Table 2.
A PLUTON[36] drawing is shown in Figure 2.

Table 2: *Crystal data and structure refinement for compound* **5**

Crystal color	transparent colorless
Crystal shape	rather regular fragment
Size [mm]	0.52 x 0.36 x 0.17 mm
Empirical formula	$C_{20}H_{22}N_2O_5S$
Molecular weight	402.46 g.mol^{-1}
Temperature	293(2) K
Radiation / wavelength	MoKα (graphite mon.) / 0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 27.2202(11) Å α = 90°
(25 reflections, 18.431 < θ < 21.309)	b = 5.1944(4) Å β = 130.396(3)°
	c = 18.7846(7) Å γ = 90°
Volume	2022.8(2) Å^3
Z	4
Calculated density	1.322 Mg.m^{-3}
Absorption coefficient	0.193 mm^{-1}

Continuation of **Table 2**: *Crystal data and structure refinement for compound* **5**

Diffractometer / scan	Enraf-Nonius CAD4 / θ-2θ
F(000)	848
θ-range for data collection	2.85 - 26.31°
Index ranges	$-25 \le h \le 33$, $0 \le k \le 6$, $-23 \le l \le 0$
Reflections collected / unique	2362 / 2293 [R(int) = 0.0123]
Reflections observed	2112 ($[I_o > 2\sigma (I_o)]$)
Absorption correction	Semi-empirical from ψ-scans
Range of rel. transm. factors	1.019 and 0.983
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2293 / 1 / 342
Goodness-of-fit on F^2	1.023
SHELXL-97 weight parameters	0.036400 0.560700
Final R indices [I > 2σ(I)]	$R_1 = 0.0266$, $wR_2 = 0.0660$
R indices (all data)	$R_1 = 0.0304$, $wR_2 = 0.0682$
Extinction coefficient	0.0017(5)
Largest difference peak and hole	0.162 and -0.099 e.Å^{-3}

3.6 References and notes

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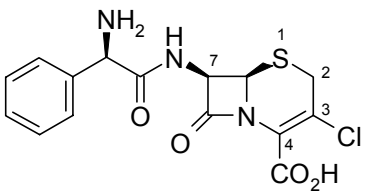
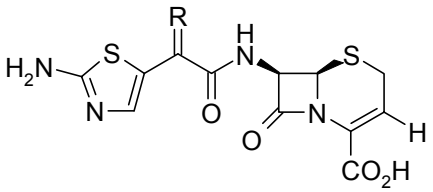
4 A SYNTHETIC STUDY TOWARDS 3-NORCEPHALOSPORINS: BARTON'S RADICAL DECARBOXYLATION REACTION IN CEPHALOSPORIN CHEMISTRY

4.1 Introduction

3-Norcephalosporins bearing hydrogen or a heteroatom at the C_3 position are an important class of β-lactam antibiotics. They generally show a high biological activity and as a medicine they can be administered orally.[1],[2] Important examples are cefaclor (**1**), ceftibuten (**2**) (R=CH(CH_2CO_2H)) or ceftizoxime (**3**) (R=N(OCH_3)) (Figure 1).



1 cefaclor

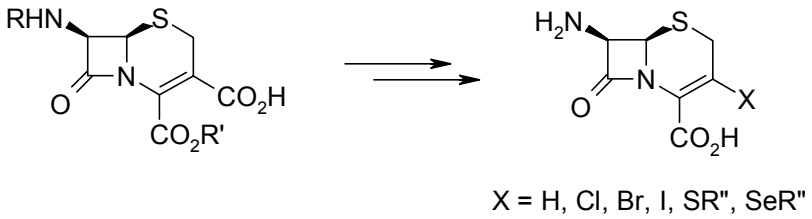


2 ceftibuten (R=CH(CH_2CO_2H))
3 ceftizoxime (R=N(OCH_3))

Figure 1.

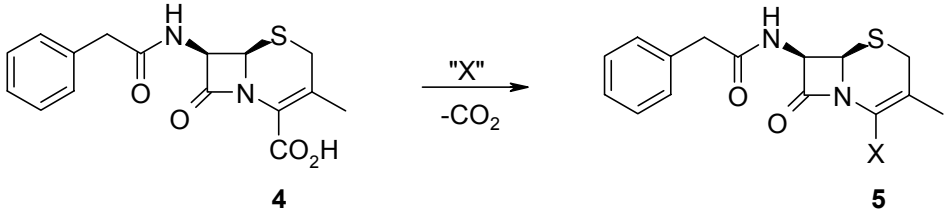
So far, the reported syntheses of such 3-norcephalosporins mainly rely upon replacement of the C_3-hydroxyl group in 3-hydroxy-ceph-3-em-4-carboxylates, which are derived from either natural penicillins or cephalosporins.[1],[3],[4] These excellent and high-yielding approaches, however, involve sophisticated and hazardous operations and/or are accompanied by undesired Δ^3/Δ^2-migration of the double bond. Syntheses of the 3-unsubstituted ceph-3-ems have been reported before and the preferred routes are either *via* 3-*exo*methylene cephem derivatives[5] or *via* 3-hydroxy-3-cephem derivatives.[1],[3],[6]

In order to evaluate alternative and more efficient routes to these 3-functionalised cephalosporins, (halo)-decarboxylation reactions of suitably substituted carboxycephalosporin molecule (*vide infra*) was studied. The attractive feature of this approach is that the removal of the carbon atom and the introduction of the heteroatom takes place simultaneously in one synthetic operation (Scheme 1). Eventually, the results of this study may result in a new route to 3-norcephalosporins from 3-carboxycephalosporins.



Scheme 1.

When this study started, the required 3-carboxycephems were not readily available. Recently however, a new and improved synthesis of these molecules was developed (see Chapter 5).[7] 7-Aminodesacetoxy-cephalosporanic acid (7-ADCA) (**4**), protected as a phenylacetyl amide, was chosen as a model compound for this halo-decarboxylation study (Scheme 2). This molecule contains the essential α,β-unsaturated carboxylic acid functionality in a β-lactam nucleus, and the compound can easily be obtained by fermentation.[8]



4 **5**

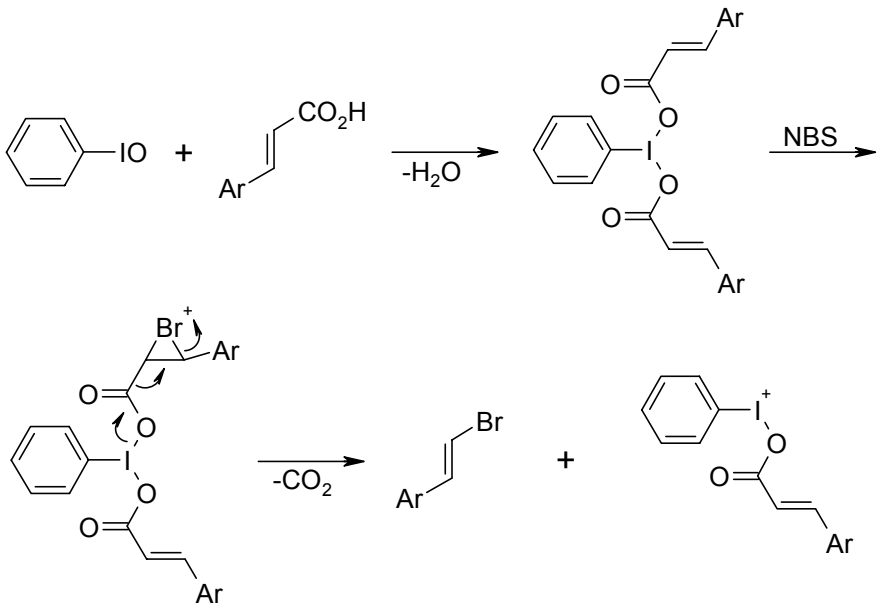
Scheme 2.

4.2 Overview of the relevant literature

The decarboxylation of organic carboxylic acids, which is accompanied by a concurrent replacement by a halogen, is an extremely useful and selective methodology for the synthesis of halogenated organic substances. The first and most well-known example of a halo-decarboxylation is the Hunsdiecker reaction. In this reaction the silver salt of a carboxylic acid is heated in the presence of halogen to give the corresponding halo compound. Later a number of other more efficient and selective methods was developed.[9] In general, the (halo)-decarboxylation reaction can either proceed *via* an ionic or a radical mechanism. Both approaches will be discussed below.

Non-radical approach

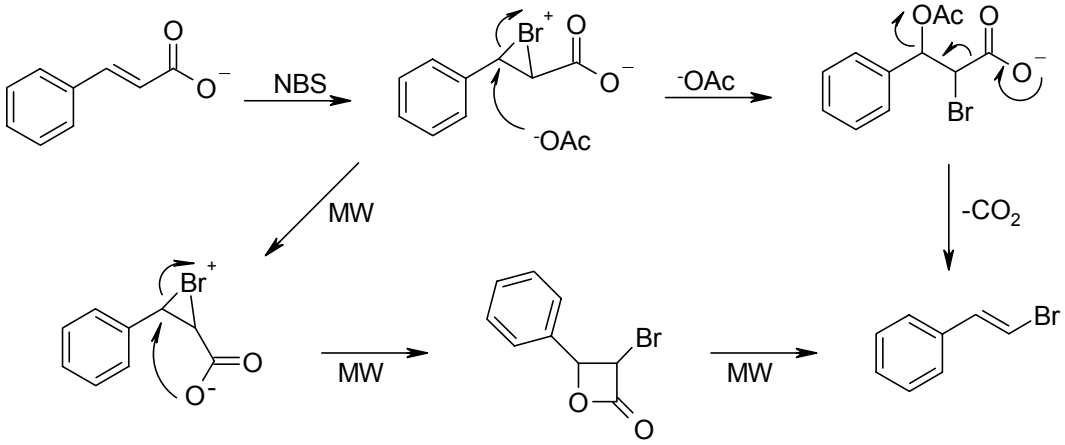
While the classical Hunsdiecker reaction involves a radical pathway, recently, a synthetic procedure for the oxidative bromo-decarboxylation of α,β-unsaturated carboxylic acids under non-radical conditions has been described.[10] This method uses iodosylbenzene or iodosylbenzene diacetate and *N*-bromosuccinimide (NBS) as the halogen donor. A major drawback of this method is that only compounds bearing an aromatic substituent at the β-position (cinnamic acid derivatives) gave good results (yields 31-78%). The tentative mechanism of this reaction is depicted in Scheme 3.



Scheme 3.

The corresponding chloro- or iodo-decarboxylation products could be obtained using *N*-chlorosuccinimide or *N*-iodosuccinimide as the halogen source, although the yields were generally lower than for the bromo variant. Substrates bearing an alkyl group at the β-position were not very reactive and only a trace amount of the bromo-decarboxylation product was formed.

More recently, Chowdhury *et al*. performed non-radical Hunsdiecker reactions on α,β-unsaturated carboxylic acids in a catalytic fashion, using less hazardous conditions than needed for the classical Hunsdiecker reaction.[11],[12] A conceptually simple strategy employing *in situ* generated metal carboxylates yielded β-halostyrenes from the corresponding α,β-unsaturated aromatic carboxylic acids using *N*-halosuccinimides as the halogen source and Group-1 metal acetates as the catalysts. Recently, this reaction has also been carried out using microwave conditions.[13] Two possible mechanisms, *via* an ionic pathway, have been reported for this reaction (Scheme 4).



Scheme 4.

The lithium acetate assisted mechanism is observed at room temperature, whereas the mechanism *via* the thermal decomposition of the intermediate β-lactone is suggested to occur under microwave conditions.[12],[13] The thermal decomposition of β-lactones is a well-established method for the synthesis of substituted alkenes.[14]

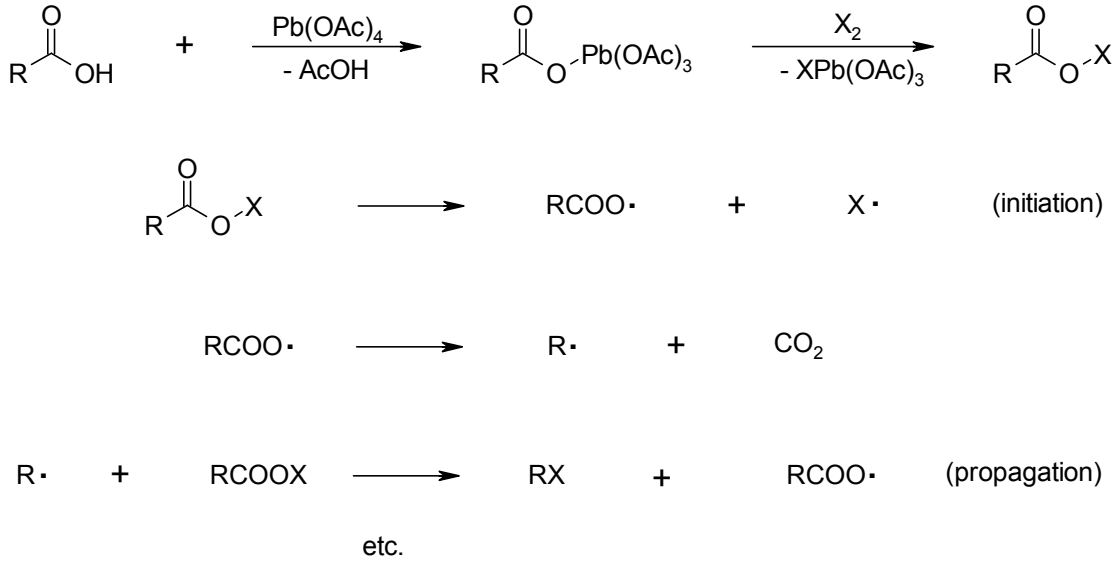
A nitrone trapping experiment indicated a predominance of the abovementioned ionic pathway over a possible radical route. In another communication, the first example of a metal-free Hunsdiecker reaction, catalyzed by tetrabutylammonium trifluoroacetate, was reported.[15] A limitation of this method is that only for α,β-

unsaturated carboxylic acids, bearing aromatic groups at the β-position, good yields of the corresponding halides were obtained.

Radical approach

The generation of carboxyl radicals requires the preparation of suitable precursors containing a weak carboxyl-X bond susceptible to homolytic cleavage. In the classical Hunsdiecker reaction, the precursor is an acyl hypo halite (X is halogen). More recently, the acylhalites are prepared *in situ* by reaction of a metal salt of the carboxylic acid with a halogen. Originally, silver salts were used, but problems associated with the preparation of dry silver carboxylates, as well as the high costs, have led to the development of methods using mercury and thallium salts.[16]

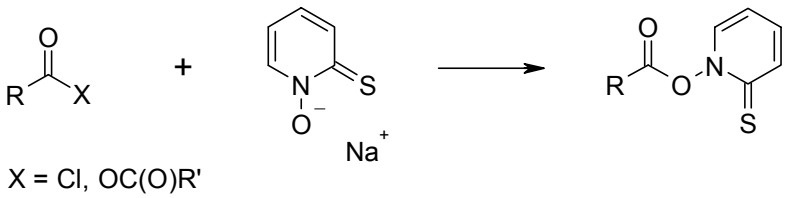
Also lead(IV) carboxylates are used as precursors for the homolytic cleavage reaction. The generation of lead(IV) carboxylates involves exchange of an acetate of lead(IV) acetate (LTA) for the acid to be decarboxylated. The weak bond to be cleaved is a carboxyl-lead(IV) bond. The higher activation energy for decarboxylation of acetoxyl radicals ensures preferential decarboxylation of most alkanoic acids. On the other hand, attempts to decarboxylate of aryl acids fail due to competing acetoxyl decarboxylation.[9] The mechanism of this modified Hunsdiecker reaction is believed to be as follows (Scheme 5):



Scheme 5.

Recently, methods have been devised for carboxyl radical generation by homolytic cleavage of weak carboxyl-N single bonds. Such methods have great potential in organic synthesis since the generation requires neither strong oxidants nor strong

electrophilic species. Such precursors are therefore compatible with a large range of functional groups. The method most commonly employed involves the use of *O*-acyl thiohydroxamates. These compounds are generally prepared by reaction of acyl chlorides or mixed anhydrides with the commercially available sodium salt of 2-mercapto-pyridine-*N*-oxide (Scheme 6).[16]



Scheme 6.

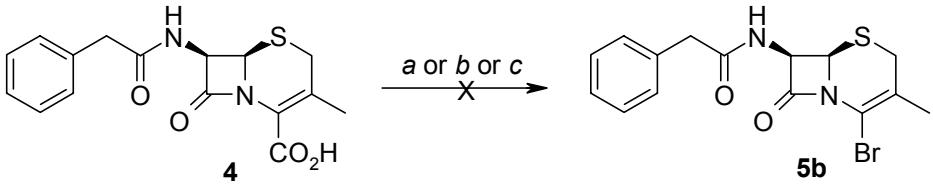
This radical chain decarboxylation process, resulting from the thermal or photochemical decomposition of thiohydroxamic esters, is better known as Barton's radical decarboxylation reaction. A variety of aromatic and vinylic acids has been decarboxylated by an adaptation of this method involving the use of AIBN as the radical chain initiator. Hence, this procedure has prospects for the (halo)-decarboxylation of the cephalosporin molecules.[17],[18]

In this chapter studies concerning the (halo)-decarboxylation of model compound 7-phenylacetyl-ADCA **4**, applying the above-mentioned methods, will be described.

4.3 Results and discussion

Non-radical approach

First the oxidative halo-decarboxylation using iodosylbenzene or iodosylbenzene diacetate and *N*-halosuccinimide, a procedure which gave good results for a limited number of α,β-unsaturated carboxylic acids,[10] was tried with 7-phenylacetyl-ADCA **4** as the substrate in order to synthesize 4-norcephalosporins **5** (Scheme 7). Unfortunately, no decarboxylation reaction did take place according to TLC analysis. Presumably, halogenation of the starting material had occurred instead of decarboxylation. Even an excess of *N*-halosuccinimide or longer reaction times did not lead to any decarboxylation product.



a) 0.5 equiv. iodosylbenzene diacetate, CH_3CN / H_2O (2:1), NBS, 60°C, 30'; b) NBS, $Mn(OAc)_2$ (0.1 equiv.), CH_3CN / H_2O (1:1), r.t., 16h; c) LiOAc (0.1 equiv.), CH_3CN / H_2O (1:1), NBS, 8h.
Scheme 7.

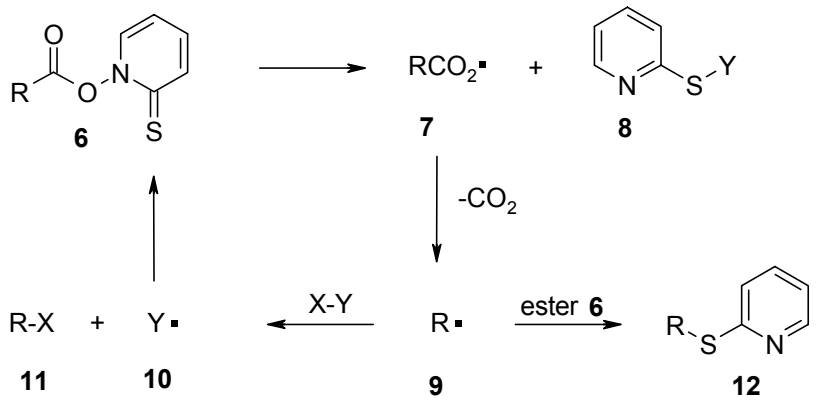
Using the procedures of Chowdhury *et al.*,[11],[12],[15] in which the non-radical Hunsdiecker reaction on α,β-unsaturated carboxylic acids is performed in a catalytic fashion, was also not successful. TLC analysis did not show any of the desired products. Therefore, it can be concluded that a non-radical approach is not likely to work for substrates of type **4**. The conditions as used in the ionic decarboxylation reactions cannot be applied to the rather complicated and sensitive cephalosporin system without major changes. Therefore, more attention was paid to the radical approach of the decarboxylation reaction of **4**.

Radical approach

The classical Hunsdiecker conditions are not suitable for the halo-decarboxylation of **4**. It is obvious that methods using molecular halogen as the halogen radical source cannot be applied for the halo-decarboxylation of **4** because of the presence of the olefin moiety. Furthermore, ring-opening reactions have been reported when molecular chlorine was brought into reaction with a penicillin molecule.[19] Moreover, the use of lead(IV) acetate in the presence of metal halides does not seem a good choice because this aggressive reagent causes unwanted side reactions and the work-up is usually troublesome.[20] A typical example is the unwanted Pummerer rearrangement at the sulfide of the cephalosporin, which takes place when the rather sensitive cephalosporin system is treated with lead(IV) acetate.[19] Finally, the most important limitation is the reported poor synthetic efficiency for α,β-unsaturated carboxylic acids (cinnamic acid derivatives).[17],[20] Therefore, no experimental attention was paid to the radical Hunsdiecker reaction and its variants.

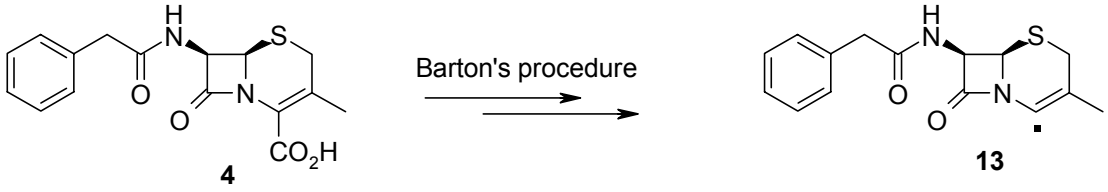
The radical chain decarboxylation process involving the thermal or photochemical decomposition of thiohydroxamic esters, as developed by Barton *et al.*,[17],[21] seems a suitable method for the halo-decarboxylation of **4**, as milder reaction conditions are used and no free halogen is present. It is assumed that the thermal or photochemical decomposition of the thiohydroxamic esters initially produces carboxyl radical **7**,

which then rapidly decarboxylates to the corresponding carbon radical **9** (Scheme 8). In the presence of an efficient radical trapping agent X-Y, substitution takes place to give **11** and a new radical **10**. Reaction of this radical **10** with **6** leads to propagation of this chain process. In the absence of an efficient trapping agent propagation occurs by reaction of the carbon radical **9** with the thiohydroxamic ester **6** leading to pyridyl sulfide **12**. The attractive features of Barton's radical decarboxylation process are its synthetic scope and the relatively mild reaction conditions. By varying the radical trapping agent X-Y, in principle a great variety of different substitution products **11** can be obtained.[22]



Scheme 8.

When this mechanism is projected on the decarboxylation of 7-phenylacetyl-ADCA **4**, the intermediate formation of vinylic radical **13** is expected (Scheme 9). Usually formation of vinylic radicals is rather difficult and requires harsh conditions.

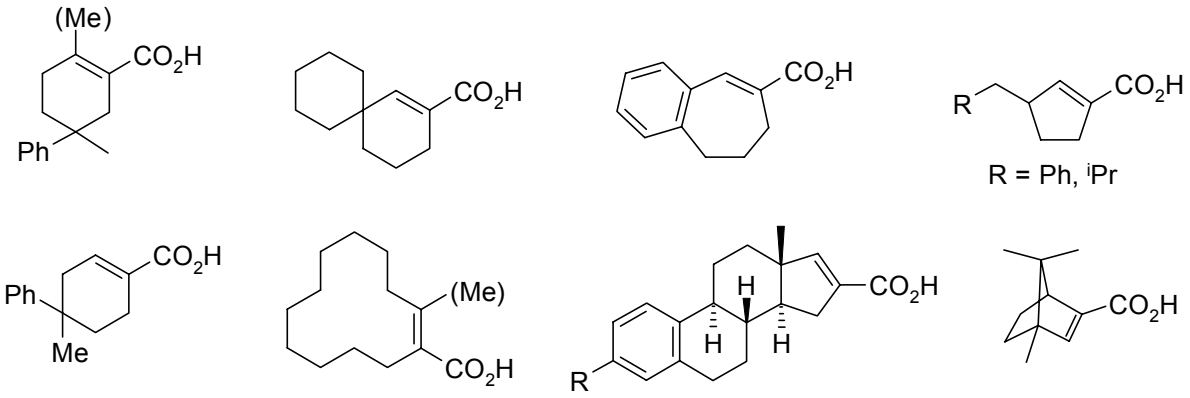


Scheme 9.

This vinylic radical may exhibit a high reactivity since it is not stabilized by any conjugation. Thus, the decarboxylation of vinylic carboxylic acids requires, as does the decarboxylation of aromatic acids, a high activation energy. Therefore, the yields of the vinylic type of decarboxylation products are generally low.[20] This is illustrated by the reluctance of aromatic acids to undergo radical type decarboxylation. Once the vinylic radical **13** is formed it presumably reacts with any trapping agent available in the reaction mixture. This would be beneficial for the

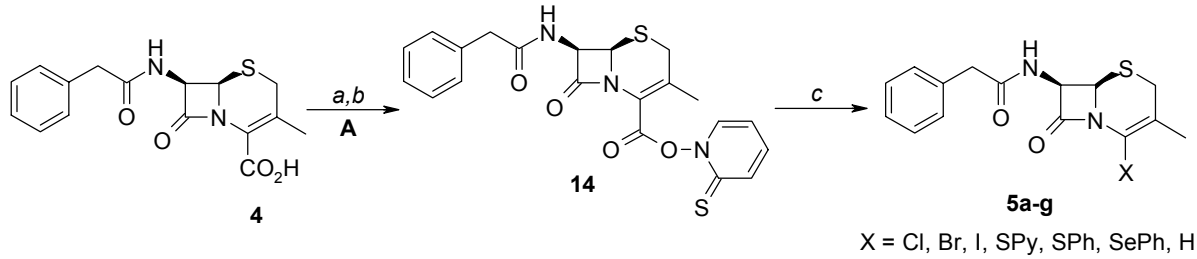
scope of such radical reactions in the cephalosporin system. Thus, the conceivable occurrence of such vinylic radicals **13** may extend this Barton methodology to cephalosporins. This would considerable enhance the scope of Barton's radical decarboxylation reaction.

Even though Barton's radical decarboxylation reaction is a well-studied reaction and is rather general applicable for primary, secondary, tertiary aliphatic acids, and to some extent also for aromatic acids, not much attention has been paid to the α,β-unsaturated acids.[23] Only a few examples of its application to α,β-unsaturated acids (mainly cinnamic acid or benzoic acid derivatives) are described.[10] The yields of the corresponding decarboxylation products, mostly bromides, are usually low. The few examples, in which reasonable yields have been reported, are collected below.[24] Clearly, these substrates do not contain additional functionalities that may cause unwanted side reactions. This in sharp contrast to cephalosporins, which have the sensitive β-lactam ring in addition to the vulnerable sulfur atom.



Initially, route **A** using thiohydroxamic ester **14** was examined (Scheme 10). The required ester was prepared by converting acid **4** into the corresponding acyl chloride using oxalyl chloride, followed by treatment with the sodium salt of *N*-hydroxypyridine-2-thione (Scheme 10). Usually, such so-called Barton esters are rather unstable compounds.[25] Due to its presumed instability, thiohydroxamic ester **14** was immediately subjected to the radical decarboxylation conditions. In order to get insight in the reaction conditions and the efficiency of this radical decarboxylation process, the replacement of the carboxylic acid moiety by bromide was studied first. This type of trapping reaction usually gives good to excellent yields. For this purpose **14** was heated in bromotrichloromethane at reflux, while irradiating with a tungsten lamp. In this reaction the solvent bromotrichloromethane

also acts as the trapping agent. Although TLC analysis showed no starting material anymore, the yield of bromo-decarboxylation product **5b** was disappointing (8-10%).



a) oxalyl chloride, CH_2Cl_2, 0 °C, 30', 81%; b) 1 equiv. Barton reagent (Na-salt), CH_2Cl_2, r.t., overnight, 95%; c) radical trap (solvent), reflux, 30% AIBN, 30'.

Scheme 10.

Table 1: *Results of Barton's radical decarboxylation reactions from ester **14***

entry:	product:	trapping agent:	product (-X):	% yield method A:
1	**5a**	CCl_4	Cl	9
	5g			9
	14			50
2	**5b**	$CBrCl_3$	Br	60
3	**5c**	CHI_3	I	80
4	**5d**	$(PhSe)_2$	SePh	34[a]
5	**5e**	$(PhS)_2$	SPh	38[a]
	5g		H	9
6	**5f**	-	Spy	20[b]
	5g		H	16
7	**5g**	*tert*-BuSH	H	30

[a] Decomposition during chromatography; TLC analysis showed a yield > 70%

[b] Product thermally unstable (decomposition under reaction conditions)

Barton *et al*. already reported that decarboxylation reactions of aromatic thiohydroxamic esters gave relatively low yields of the corresponding bromo-decarboxylation products.[23] The thiohydroxamic ester concentration builds up as a result of a relatively slow decarboxylation step of the carboxylic radical (according to Scheme 8). Once the reactive vinylic radical is formed, a highly efficient propagation process takes place in which the vinylic radical attacks the Barton ester leading to the formation of sulfide **12** in a large amount (Scheme 8). In the present case, the formation of pyridyl sulfide **5f** would be expected. However, no sulfide **5f** was isolated.

The following reasoning can be put forward to improve the Barton reaction. By generating more trichloromethyl radicals, the concentration Barton ester **14** during the reaction would decrease and hence favor the desired pathway, thereby suppressing unwanted side reactions leading to pyridyl sulfide **5f**. Indeed, prior addition of the external radical initiator AIBN (30-60%) to the reaction mixture in order to accelerate the decomposition of the thiohydroxamic ester **14** and to avoid the formation of sulfide **5f**, resulted in a more efficient attack of the vinylic radical to ester **14**. A remarkable improvement from 8 to 50% yield of bromide **5b** was achieved in this manner.

In contrast with the published examples, it appeared possible to isolate thiohydroxamic ester **14** which proved to be stable at room temperature for several weeks. The use of the more pure ester in the Barton decarboxylation process led to an extra improved product formation. Bromide **5b** was now obtained in yields up to 60% (Table 1).

The halo-decarboxylation reaction of **14** was studied under standard conditions with a variety of trapping agents. All results are collected in Table 1. For the synthesis of 4-chloro-7-ADCA **5a** a solution of thiohydroxamic ester **14** in dichloromethane was added dropwise to a solution of AIBN in a mixture of chlorobenzene and tetrachloromethane under reflux, while irradiating with a tungsten lamp. A mixture of two products together with some starting material was obtained from which the desired chloride **5a** was isolated in only 9%. The second product was identified as the parent β-lactam skeleton **5g** (9% yield), while 50% of starting material **14** was recovered (Table 1). The nature of the trapping agent is the major factor that causes a lower yield for the chloro-decarboxylation as compared with the bromo-decarboxylation. It is energetically more difficult to break a C-Cl bond (*e.g.* in CCl_4) than a C-Br bond (*e.g.* in $CBrCl_3$). Therefore, trapping of the vinyl radical is less efficient for organic chlorides, and the yield of the corresponding chloride is consistently lower than that of the corresponding bromide.

Attempts to improve the formation of chloride **5a** by using other chlorine donors as trapping agents (*e.g.* NCS or *tert*-butyl hypochorite,[25] trityl chloride, Cl_3CSCl, hexachloroacetone) did not meet with success. Sonication-induced halo-decarboxylation, as was described by Dauben *et al.*,[26] in some cases leads to a better yield of the corresponding chloro-decarboxylation products. The ultrasonic irradiation (20 kHz, <60 W / cm^2) of thiohydroxamic ester **14** or **15** (Scheme 13) in

CCl_4 at room temperature did not show any reaction at all, whereas irradiation in $BrCCl_3$ after 10 minutes gave complete conversion to bromide **5b** (TLC analysis). Apparently, ultrasound is capable to produce trichloromethyl radicals from bromotrichloromethane, but not from tetrachloromethane. This result convincingly demonstrates that the reluctance of the C-Cl bond cleavage in the trapping agent under the conditions applied, is the major factor that is responsible for the inefficiency of this chloro-decarboxylation process. As may be expected on the basis of the relative weakness of the C-I bond, an excellent result was obtained for the iodo-decarboxylation of **14**, when iodoform was used as the trapping agent. By generating radical **13** in chlorobenzene in the presence of a large excess of iodoform iodide **5c** was obtained in a yield of 80% (Table 1).

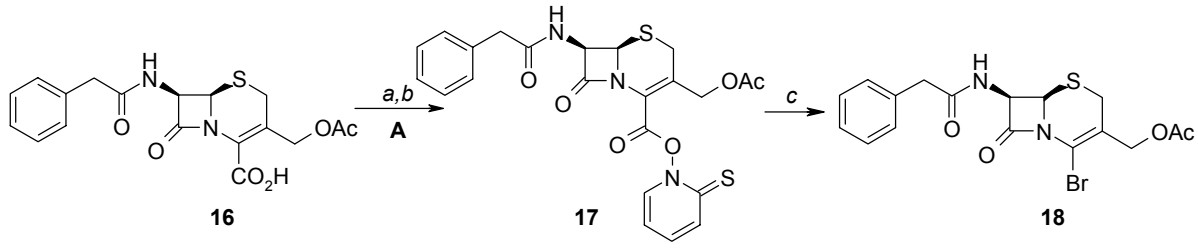
Having successfully accomplished the halo-decarboxylation of acid **4** using Barton's procedure, the question arose whether this methodology would be applicable for the introduction of other heteroatom containing substituents at the C_4 position. The formation of pyridyl sulfide **12** (see Scheme 8) usually takes place in the absence of a radical trap.[25] In the present case, pyridyl sulfide **5f** could be readily synthesized by heating ester **14** in refluxing chlorobenzene in the presence of AIBN as the radical initiator. This sulfide **5f** appeared to be thermally unstable under the reaction conditions used, and therefore the yield of the isolated product was only 20% (Table 1). The second product was *β*-lactam **5g** (16% yield) in which the carboxylic group is replaced by a hydrogen atom. The inherent instability of pyridyl sulfide **5f** may be the reason that this product could not be isolated in other trapping experiments.

The radical chalcogenation of a variety of carboxylic acids has already been studied by Barton *et al.*[27] and was shown to proceed quite well in many cases, depending on the efficiency of the trapping agent used. When diphenyl disulfide or diphenyl diselenide was used as the trapping agent under standard reaction conditions, radical decarboxylation of **4** led to phenylsulfide **5e** or its selenium analogue **5d** in 38% and 34% yield, respectively (Table 1). In the case of diphenyldisulfide as the trapping agent, in addition of sulfide **5e** also 9% of parent compound **5g** was isolated. TLC analysis, however, showed conversions of higher than 70%, indicating considerable decomposition of the products. The sulfur and selenium containing products were indeed rather unstable. During purification *via* column chromatography over silica gel considerable loss of products had to be accepted. These results show that the disulfide bond and diselenide bond in the trapping

agents are weak enough to compete with the thiohydroxamic ester in trapping the vinylic radical **13**.

The product **5g**, which essentially is the result of a decarboxylation, could be obtained more efficiently using *tert*-butyl mercaptane as the trapping agent under standard conditions (30% yield; Table 1).

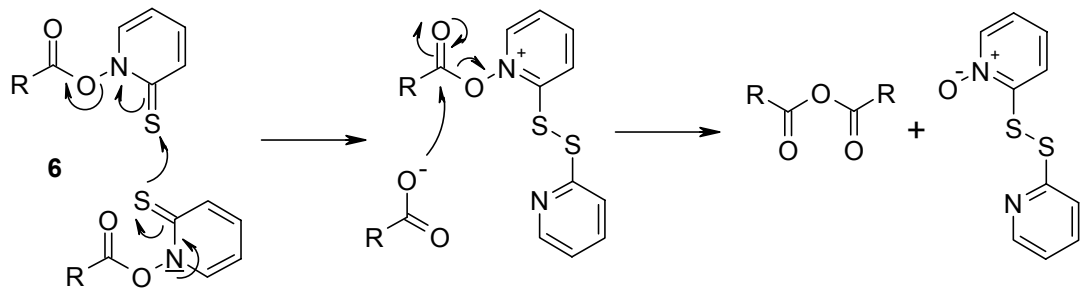
In order to establish the scope of the Barton reaction, 7-ACA **16** (containing an acetate group at the C_{10} position) was also subjected to the Barton decarboxylation procedure (Scheme 11). The presence of the relative labile acetate group caused no problems in the case of the bromo-decarboxylation, as bromide **18** was obtained in 65% using method A. This finding is very pleasing as the acetate group can be used for further synthetic elaboration at the C_{10} position, and thereby allowing the synthesis of a variety of 4-halo-3-substituted cephalosporins.



a) oxalyl chloride, CH_2Cl_2, 0 °C, 30', 70%; b) 1 equiv. Barton reagent (Na-salt), CH_2Cl_2, r.t., overnight, 97%; c) radical trap (solvent), reflux, 30% AIBN, 30', 65%.

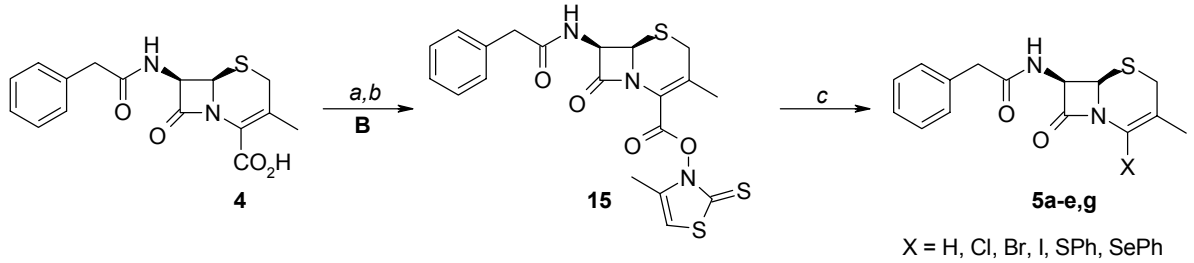
Scheme 11.

The only literature, examples, which led to efficient decarboxylation of *α,β*-unsaturated acid derivatives, all involve slightly different thiohydroxamic esters (derived from *N*-hydroxy-4-methyl-2-thiazolinethione).[24],[28],[29] In earlier studies,[29],[30] these readily available compounds were found to be much less sensitive to visible light and significantly more robust towards hydrolysis. This would allow a slow generation of radicals without unwanted ionic side reactions, usually caused by anhydride formation, as shown in Scheme 12.[17]



Scheme 12.

After optimization experiments, the best results were obtained using the slightly modified Barton ester **15** (Scheme 14). This ester appeared to be more stable than **14** and could be handled better in the subsequent decarboxylation reactions.[28] An additional advantage is the decreased formation of very polar products (TLC analysis), caused by decomposition of the thiohydroxamic ester *via* an ionic pathway (Scheme 12).[17] The results of the radical decarboxylation reactions using ester **15** (route **B**) are collected in Table 2.



a) oxalyl chloride, CH_2Cl_2, 0 °C, 30', 81%; b) 1.0 equiv. Barton reagent (alcohol), CH_2Cl_2, r.t., overnight, 96%; c) radical trap (solvent), reflux, 30% AIBN, 30'.

Scheme 13.

Table 2.: *Results of Barton's radical decarboxylation reactions from esters **14** and **15***

entry:	trapping agent:	product:	product (-X):	% yield method A:	% yield method B:
1	CCl_4	**5a**	Cl	9	12
		5g	H	9	9
		14 or **15**		50	60
2	$CBrCl_3$	**5b**	Br	60	80
3	CHI_3	**5c**	I	80	80
4	$(PhSe)_2$	**5d**	SePh	34[a]	21[a]
5	$(PhS)_2$	**5e**	SPh	38[a]	28[a]
		5g	H	9	
6	-	**5f**	Spy	20[b]	-[c]
		5g	H	16	
7	*tert*-BuSH	**5g**	H	30	46

[a] decomposition during flash chromatography; TLC analysis showed a yield > 70%

[b] product thermally unstable (decomposition under reaction conditions)

[c] not performed

The data in this Table reveal that in most cases the yields of the decarboxylation products using ester **15** are significantly higher. Especially the introduction of bromine and iodine appears to be more efficient, whereas the introduction of hydrogen and chlorine is still troublesome. The lower yields observed for the

formation phenylsulfide **5e** and phenylselenide **5d** are probably not the result of lower product efficiency in the radical decarboxylation process, but are most likely due to the instability of these compounds on silica gel (*vide supra*).

4.4 Concluding remarks

The results described in this chapter show that radical decarboxylation reactions using Barton's thiohydroxamic radical chemistry is successful in cephalosporin molecules. Other methods, following non-radical approaches all failed. Starting from the model substrate 7-phenylacetyl-ADCA **4**, and using the slightly modified thiohydroxamic ester **15**, a variety of 4-functionalised cephalosporins has been synthesized. It should be noted that this successful radical approach to the halo-decarboxylation is highly remarkable for the sensitive β-lactam system. The only drawback is the rather low efficiency for the introduction of chloride. However, this is a general phenomenon in the Barton halo-decarboxylation, and due to the relatively high stability of the organic chlorine donors. The results of this model study offer good prospects for a functionalization of cephalosporins at the C_3-position leading to the important 3-norcephalosporins (including 3-halocephalosporins), using this Barton radical decarboxylation methodology.

4.5 Experimental part

General remarks

100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer and 300 MHz ^{1}H-NMR spectra and all ^{13}C-NMR spectra were recorded on a Bruker AC 300 using Me_4Si as internal standard. All coupling constants are given as ^3J in Hz, unless indicated otherwise. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FTS-25 instrument. For mass spectra a double focusing VG7070E mass spectrometer was used. For some samples, High Resolution FAB was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer (JEOL Ltd. 1-2 Musashino 3-chome, Akishima Tokyo), coupled to a MS-MP 9021D/UPD data system (University of Amsterdam). Elemental analyses were conducted on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. For the determination of optical rotations a Perkin-Elmer 241 polarimeter was used. Solvents were dried using the following methods: dichloromethane was distilled from P_2O_5; ethyl acetate was distilled from K_2CO_3; diethyl ether was distilled from NaH; hexane and heptane were distilled from CaH_2. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on a Merck precoated silica gel 60 F254 plates (0.25 mm). Spots were visualized with UV or using a molybdate spray. Flash chromatography was carried out at a pressure of *ca*. 1.5 bar, using Merck Kieselgel 60H. Column

chromatography at atmospheric pressure was performed with ACROS silicagel (0.035-0.070 mm; pore diameter ca. 6 nm).
Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada).

(7*R*,7a*R*)-3-Methyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carbonyl chloride (4a)

To a solution of 7-phenylacetyl-ADCA **4** (10.0 g; 0.0312 mol) in dichloromethane (250 ml) was added oxalyl chloride (3.6 ml; 1.3 equivalents) and a few drops of DMF. After stirring for ca. 1h, the reaction mixture became clear. Then two volumes of hexane (300 ml) were added. The resulting precipitate was collected by filtration, washed with hexane and dried *in vacuo*. The crude acid chloride **4a** (8.60 g; 81% yield) was used for reactions without further purification.

General procedure for the radical decarboxylation reactions (1.0 mmol scale)

Thiohydroxamic ester **14, 15** or **17** in dichloromethane (3-5 ml) protected from light was gradually added in 15-30 min. to a solution of trapping agent in an appropriate solvent (or trapping agent only) containing radical initiator AIBN (0.055 g; 0.3 mmol). During the addition, the reaction mixture was heated at reflux (or 110 °C) under nitrogen and irradiated with a 250 W tungsten lamp. Then the reaction mixture was stirred for another 10 minutes, cooled to room temperature and concentrated under reduced pressure. The crude product was purified *via* flash chromatography over silica gel, followed by recrystallisation.

***N*1-[(7*R*,7a*R*)-4-Chloro-3-methyl-6-oxo-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazin-7-yl]-2-phenylacetamide (5a)**

Following the general procedure (Barton ester **15**, addition time: 25 min., chlorobenzene as solvent and tetrachloro methane as trapping agent (v/v = 1/1)), flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:1) gave **5a** as a slightly yellow solid (0.076 g; 12%) and **5g** (0.054 g; 9%) and starting thiohydroxamic ester **15** (60%).
Mp 194-196°C (dec.); $[\alpha]_D$ = +150° (c = 0.11; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.85 (s, 3H, CH_3), 3.09 and 3.49 (qAB, J_{AB} = 17.3 Hz, 2H, SCH_2), 3.64 (s, 2H, $PhCH_2$), 5.01 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 5.76 (dd, *J* = 4.8 Hz *J* = 9.0 Hz, 1H, NHC*H*CHS), 6.35 (d, *J* = 9.0 Hz, 1H, NH), 7.31 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 18.7 (CH_3), 30.0 (SCH_2), 43.4 ($PhCH_2$), 59.3 (CHNH), 59.6 (CHS), 115.0 (=CCl), 119.5 (=*C*(CH_3)), 127.8, 129.2, 129.5 and 133.5 (PhC), 164.1 (C=O, lactam), 171.1 ($PhCH_2$*C*(O)); IR (KBr): ν 3266 (broad, NH), 1777 (C=O, lactam), 1661 and 1535 (C=O, amide), 1340 (CN) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 345 (4) $[M+Na]^+$, 323 (22) $[M+H]^+$, 289 (8) $[M+H-Cl]^+$, 57 (100); HRMS (CI$^+$, m/z): calculated for $C_{15}H_{16}O_2N_2SCl$: 323.06210 amu. Found: 323.06194 ± 0.00097 amu.

***N*1-[(7*R*,7a*R*)-4-Bromo-3-methyl-6-oxo-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazin-7-yl]-2-phenylacetamide (5b)**

Following the general procedure (Barton ester **15**, addition time: 15 min., bromotrichloromethane (15 ml) as trapping agent, flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:1) resulted, after crystallization (hexane / ethyl acetate), in **5b** (0.293 g; 80%) as white needles.

Mp 156-157°C; $[\alpha]_D$ = +42° (c = 0.1; $CHCl_3$); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.86 (s, 3H, CH_3), 3.12 and 3.50 (qAB, J_{AB} = 17.4 Hz, 2H, SCH_2), 3.64 (s, 2H, $PhCH_2$), 5.03 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.75 (dd, *J* = 4.7 Hz *J* = 9.0 Hz, 1H, NHC*H*CHS), 6.17 (d, *J* = 9.0 Hz, 1H, NH), 7.32 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 21.3 (CH_3), 30.3 (SCH_2), 43.3 ($PhCH_2$), 59.3 (CHNH), 59.9 (CHS), 107.6 (=CBr), 118.5 (=*C*(CH_3)), 127.7, 129.2, 129.5 and 133.6 (PhC), 164.3 (C=O, lactam), 171.1 ($PhCH_2$*C*(O)); IR (KBr): ν 3265 (broad, NH), 1768 (C=O, lactam), 1649 and 1535 (C=O, amide), 1340 (C-N) cm^{-1}; MS (EI$^+$): *m/z* (%) = 366 (<1) and 368 (<1) [M$^+$], 338 (2) and 340 (2) [M-CO]$^+$, 259 (11) [M-CO-Br]$^+$, 91 (100) [$PhCH_2$]$^+$; elem. anal.: calc. (found) for $C_{15}H_{15}O_2N_2SBr$: C: 49.06 (49.06), H: 4.12 (4.14), N: 7.63 (7.54), S: 8.43 (8.69).

N1-[(7*R*,7a*R*)-4-Iodo-3-methyl-6-oxo-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazin-7-yl]-2-phenylacetamide (5c)

Following the general procedure (Barton ester **15**, addition time: 25 minutes, chlorobenzene (5 ml) as solvent, iodoform (1.18 g; 3 equiv.) as trapping agent dissolved in chlorobenzene (10 ml), flash chromatography (SiO_2, *n*-hexane/ethyl acetate 1:1) resulted, after crystallization (hexane / ethyl acetate), in iodide **5c** (0.324 g; 80%) as white needles.

Mp 158-159°C (dec.); $[\alpha]_D$ = +83° (c = 0.41; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.91 (s, 3H, CH_3), 3.20 and 3.57 (qAB, J_{AB} = 17.1 Hz, 2H, SCH_2), 3.65 (s, 2H, $PhCH_2$), 5.05 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.72 (dd, *J* = 4.7 Hz *J* = 9.0 Hz, 1H, NHC*H*CHS), 6.08 (d, *J* = 9.0 Hz, 1H, NH), 7.32 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 26.2 (CH_3), 29.9 (SCH_2), 43.4 ($PhCH_2$), 59.5 (CHNH), 60.0 (CHS), 107.3 (=CI), 124.4 (=*C*(CH_3)), 127.7, 129.2, 129.5 and 133.6 (PhC), 164.5 (C=O, lactam), 170.9 ($PhCH_2$*C*(O)); IR (KBr): ν 3280 (broad, NH), 1757 (C=O, lactam), 1655 and 1536 (C=O, amide), 1355 (C-N) cm^{-1}; ; MS (EI$^+$): *m/z* (%) = 414 (<1) [M$^+$], 386 (<1) [M-CO]$^+$, 287 (6) [M-I]$^+$, 259 (26) [M-CO-I]$^+$, 240 (50), 176 (48), 141 (24), 91 (100) [$PhCH_2^+$]; elem. anal.: calc. (found) for $C_{15}H_{15}O_2N_2SI$: C: 43.49 (43.69), H: 3.65 (3.63), N: 6.76 (6.77), S: 7.74 (8.02).

N1-[(7*R*,7a*R*)-3-Methyl-6-oxo-4-(phenylselanyl)-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazin-7-yl]-2-phenylacetamide (5d)

Following the general procedure (Barton ester **14**, addition time: 25 min., chlorobenzene (5 ml) as solvent and diphenyldiselenide (0.625 g; 2 equiv.) as trapping agent), flash chromatography (*n*-hexane / ethyl acetate 2:1) gave **5d** (0.145 g; 34%) as a white solid. The product appeared to be unstable during purification by flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:1).

Mp 118-120°C (dec.); $[\alpha]_D$ = +48° (c = 0.55; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.85 (s, 3H, CH_3), 3.49 and 3.09 (qAB, J_{AB} = 17.3 Hz, 2H, SCH_2), 3.64 (s, 2H, $PhCH_2$), 5.01 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 5.76 (dd, *J* = 4.8 Hz *J* = 9.0 Hz, 1H, NHC*H*CHS), 6.35 (d, *J* = 9.0 Hz, 1H, NH), 7.31 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.1 (CH_3), 29.6 (SCH_2), 43.2 ($PhCH_2$), 58.7 (CHNH), 59.5 (CHS), 108.2 (=*C*CH_3), 125.3 (=*C*SPh), 127.5, 127.5, 128.9, 129.2, 129.3, 129.4, 132.1, 132.2, 132.3 and 133.8 (PhC), 163.9 (C=O, lactam), 171.2 ($PhCH_2$*C*(O)); IR (KBr): ν 3273 (broad, NH), 3053 (CH, phenyl), 1761 (C=O, lactam), 1658 and 1534 (C=O, amide), 1335 (C-N) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 467 (16) [M+Na]$^+$, 445 (31) [M+H]$^+$, 416 (8) [M+H-CO]$^+$, 339 (8), 270 (56), 260 (28) [M+H-CO-SePh]$^+$, 91 (100) [$PhCH_2^+$]; elem. anal.: calc. (found) for $C_{21}H_{20}O_2N_2SSe$: C: 56.88 (56.54), H: 4.55 (4.48), N: 6.32 (6.29).

N1-[(7R,7aR)-3-Methyl-6-oxo-4-(phenylsulfanyl)-7,7a-dihydro-2H,6H-azeto[2,1-b][1,3]thiazin-7-yl]-2-phenylacetamide (5e)

Following the general procedure (addition time: 20 min., chlorobenzene (15 ml) as solvent containing diphenyldisulfide (2.18 g; 10 equiv.) thiohydroxamic ester **14** added in chlorobenzene (3 ml)), flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:1) gave **5e** (0.150 g; 38%) as a yellow-white solid and **5g** (0.027 g; 9%) as yellow-white solid.

Mp 182-184°C (dec.); $[\alpha]_D$ = +25° (c = 0.55; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 2.05 (s, 3H, CH_3), 3.17 and 3.53 (qAB, J_{AB} = 17.8 Hz, 2H, SCH_2), 3.60 (s, 2H, $PhCH_2$), 4.88 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.54 (dd, *J* = 4.8 Hz *J* = 8.9 Hz, 1H, NHC*H*CHS), 6.35 (d, *J* = 8.9 Hz, 1H, NH), 7.28 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 20.2 (CH_3), 29.9 (SCH_2), 43.2 ($PhCH_2$), 58.7 (CHNH), 59.6 (CHS), 123.1 (=*C*CH_3), 124.8 (=*C*SPh), 127.1, 127.5, 129.0, 129.4, 129.4, 129.6, 130.0, 133.3 and 133.8 (PhC), 163.7 (C=O, lactam), 171.2 ($PhCH_2$*C*(O)); IR (KBr): ν 3291 (broad, NH), 3044 (CH, phenyl), 1768 (C=O, lactam), 1660 and 1531 (C=O, amide), 1334 (C-N) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 419 (33) $[M+Na]^+$, 397 (47) $[M+H]^+$, 368 (13) $[M+H-CO]^+$, 261 (19) $[M+H-CO-SPh]^+$, 222 (73), 178 (35), 109 (26) $[SPh^+]$, 91 (100) $[PhCH_2]^+$; elem. anal.: calc. (found) for $C_{21}H_{20}O_2N_2S_2$: C: 63.61 (63.47), H: 5.08 (5.00), N: 7.06 (6.98).

N1-[(7R,7aR)-3-Methyl-6-oxo-4-(2-pyridylsulfanyl)-7,7a-dihydro-2H,6H-azeto[2,1-b][1,3]thiazin-7-yl]-2-phenylacetamide (5f)

Thiohydroxamic ester **5** (0.430 g; 1 mmol) and AIBN (100 mg) were dissolved in chlorobenzene (5 ml) and the reaction mixture was heated at reflux for 90 min. and irradiated, under nitrogen, with a 250 W tungsten lamp. Then the reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:3) which afforded **5f** (0.076 g, 20%) as an yellow-white solid.

Mp 85-87°C (dec.); $[\alpha]_D$ = +40° (c = 0.27; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 2.01 (s, 3H, CH_3), 3.21 and 3.61 (qAB, J_{AB} = 17.7 Hz, 2H, SCH_2), 3.72 (s, 2H, $PhCH_2$), 5.07 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.61 (dd, *J* = 4.7 Hz *J* = 8.8 Hz, 1H, NHC*H*CHS), 6.71 (d, *J* = 8.8 Hz, 1H, NH), 6.92-8.62 (m, 9H, PhH and -PyH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 20.3 (CH_3), 30.1 (SCH_2), 43.2 ($PhCH_2$), 58.9 (CHNH), 59.6 (CHS), 113.5 (=*C*CH_3), 120.7, 122.3 (PyC), 127.6, 129.4, 129.4 and 133.8 (PhC), 136.8 (PyC), 137.5 (=C-SPy), 149.9 (=NCH=), 156.8 (SC=N), 163.4 (C=O, lactam), 171.3 ($PhCH_2$*C*(O)); IR (KBr): ν 3258 (broad, NH), 1775 (C=O, lactam), 1659 and 1563 (C=O, amide), 1615 (SC=N), 1343 (C-N) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 398 (27) $[M+Na]^+$, 365 (1) $[M+H]^+$, 287 (3) $[M-Py]^+$, 281 (9), 221 (18), 136 (26) $[M+H-SPy-PhCH_2-CO]^+$, 57 (100); HRMS (CI$^+$, m/z): calculated for $C_{20}H_{19}O_2N_3S_2$: 398.09970 amu. Found: 398.09922 ± 0.00119 amu.

N1-[(7R,7aR)-3-Methyl-6-oxo-7,7a-dihydro-2H,6H-azeto[2,1-b][1,3]thiazin-7-yl]-2-phenylacetamide (5g)

Following the general procedure (Barton ester **15**, addition time: 25 min., chlorobenzene (10 ml) as solvent and *tert*-butylmercaptane (0.451 g; 5 equiv.) as trapping agent, AIBN (30%) added together with thiohydroxamic ester **15**), flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:1) resulted, after crystallization (hexane / ethyl acetate), in **5g** (0.129 g; 46%) as white needles.

Mp 231-233°C (dec.); $[\alpha]_D$ = -35° (c = 0.52; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.75 (s, 3H, CH_3), 2.95 and 3.45 (qAB, J_{AB} = 17.3 Hz, 2H, SCH_2), 3.64 (s, 2H, $PhCH_2$), 4.90 (d, *J* = 4.6 Hz, 1H, NHCHC*H*S), 5.70 (dd, *J* = 4.6 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.28 (d, *J* = 9.2 Hz, 1H, NH) 6.41 (s, 1H, CH=), 7.31 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 21.2 (CH_3), 28.2 (SCH_2), 43.4 ($PhCH_2$),

56.8 (CHNH), 59.0 (CHS), 109.6 (=CH), 116.4 (=*C*(CH_3)), 127.7, 129.1, 129.5 and 133.7 (PhC), 163.4 (C=O, lactam), 171.1 ($PhCH_2$*C*(O)); IR (KBr): ν 3280 (broad, NH), 1757 (C=O, lactam), 1655 and 1536 (C=O, amide), 1355 (C-N) cm^{-1}; MS (EI^+): *m/z* (%) = 288 (4) [M^+], 260 (8) [M-CO]$^+$, 176 (35), 114 (90), 91 (100), [$PhCH_2^+$]; elem. anal.: calc. (found) for $C_{15}H_{16}O_2N_2S$: C: 62.48 (62.47), H: 5.59 (5.51), N: 9.71 (9.68).

2-Thioxo-1,2-dihydro-1-pyridinyl (7*R*,7a*R*)-3-methyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (14)

To a solution of acid chloride **4a** (4.00 g; 11.8 mmol) in dichloromethane (80 ml) was added *N*-hydroxypyridin-2-thione sodium salt (1.67 g; 0.95 equiv.). After stirring at room temperature for 15h the reaction mixture was extracted with a saturated solution of $NaHCO_3$ (2x50 ml) and the organic layer was washed with brine. After drying ($MgSO_4$) and concentration *in vacuo* Barton ester **14** (5.68 g; 95%) was obtained as a strongly yellow colored solid material which was sufficiently pure for the decarboxylation reactions.

Mp 78-83°C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.18 (s, 3H, CH_3), 3.21 and 3.58 (qAB, J_{AB} = 18.7 Hz, 2H, SCH_2), 3.62 and 3,68 (qAB, J_{AB} = 16.0 Hz, 2H, $PhCH_2$), 5.07 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.85 (dd, *J* = 4.7 Hz *J* = 9.1 Hz, 1H, NHC*H*CHS), 6.56 (d, *J* = 9.1 Hz, 1H, NH), 6.65 (dt, *J* = 1.7 Hz *J* = 6.9 Hz, 1H, PyH), 7.20-738 (m, 6H, PhH, PyH), 7.69 (dd, *J* = 8.8 Hz *J* = 1.6 Hz, 1H, PyH), 7.83 (dd, *J* = 6.9 Hz ^4J = ~1.0 Hz, 1H, PyH); IR (KBr): ν 3281 (broad, NH), 3027 and 2923 (=CH-), 1774 (C=O, lactam and ester), 1650 and 1527 (C=O, amide), 1447 (CO_2-N), 1367 (C-N), 1133 (C=S) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 457 (1) [M+Na]$^+$, 434 (11) [M+H]$^+$, 154 (100) [NOBA]*, 91 (22) [$PhCH_2^+$] (* defragmentation of NOBA matrix);

4-Methyl-2-thioxo-2,3-dihydro-1,3-thiazol-3-yl (7*R*,7a*R*)-3-methyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (15)

3-Hydroxy-4-methyl-2,3-dihydro-1,3-thiazole-2-thione (0.662 g; 4.5 mmol) was added to a ice-cooled suspension of crude acid chloride **4a** (1.75 g; 5.0 mmol) in dichloromethane (50 ml). The reaction mixture was stirred for 18h at room temperature. After addition of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with dichloromethane (3x75 ml). The combined organic layers were washed with brine (1x100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified *via* column chromatography (SiO_2, ethyl acetate / heptane 1:1) to give **15** as a yellow-white solid (1.99 g; 96%).

Mp 97-98°C (dec.); $[\alpha]_D$ = -31° (c = 0.49; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.01 (s, 3H, CH_3), 3.37 and 3.55 (qAB, J_{AB} = 18.1 Hz, 2H, SCH_2), 3.49 and 3.57 (qAB, J_{AB} = 13.9 Hz, 2H, $PhCH_2$), 5.01 (d, *J* = 4.6 Hz, 1H, NHCHC*H*S), 5.57 (dd, *J* = 4.6 Hz, *J* = 8.4 Hz, 1H, NHC*H*CHS), 7.25 (m, 5H, PhH), 9.07 (d, *J* = 8.4 Hz, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 19.6, 29.2, 41.8, 57.3, 59.0, 59.1, 123.0, 126.7, 128.4, 129.2, 130.1, 136.1, 163.7, 164.5, 171.2; IR (KBr): ν 3270 (broad, NH), 3027 (=CH-), 1777 (C=O, lactam and ester), 1658 and 1530 (C=O, amide), 1366 and 1336 (C-N), 1125 (C=S) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 484 (2) [M+Na]$^+$, 462 (13) [M+H]$^+$, 329 (9) [M+H-$C_4H_6NS_2$]$^+$, 287 (10) [M+H-$C_4H_6NS_2$-CO_2]$^+$, 154 (100) [NOBA]* (* defragmentation of NOBA matrix).

(7*R*,7a*R*)-4-Chlorocarbonyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazin-3-ylmethyl acetate (16a)

This compound was prepared as described for the synthesis of acyl chloride **4a**. Starting from 7-phenylacetyl-ACA[7] **16** (2.0 g; 5.1 mmol) crude **16a** was obtained as a white/yellow solid (1.46 g; 70%), which was used without further purification.

2-Thioxo-1,2-dihydro-1-pyridinyl (7*R*,7a*R*)-3-[(acetyloxy)methyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (17)

To a solution of acid chloride **16a** (4.00 g; 11.8 mmol) in dichloromethane (80 ml) was added *N*-hydroxypyridin-2-thione sodium salt (1.67 g; 0.95 equiv.). After stirring at room temperature for 15h the reaction mixture was extracted with saturated aqueous $NaHCO_3$ and the organic layer was washed with brine. After drying ($MgSO_4$) and concentration *in vacuo*, **17** (5.80 g; 97%) was obtained as a pale yellow solid material, which was sufficiently pure for the decarboxylation reactions.

Mp 85-89°C (dec.); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 2.09 (s, 3H, C(O)CH_3), 3.42 and 3.64 (qAB, J_{AB} = 18.8 Hz, 2H, SCH_2), 3.66 (s, 2H, $PhCH_2$), 5.02 (s, 2H, CH_2OAc), 5.08 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 5.92 (dd, *J* = 4.8 Hz *J* = 9.1 Hz, 1H, NHC*H*CHS), 6.47 (d, *J* = 9.1 Hz, 1H, NH), 6.62 (dt, *J* = 8.7 Hz *J* = 1.8 Hz, 1H, PyH), 7.15-7.32 (m, 6H, PhH and PyH); 7.69 (dd, *J* = 8.7 Hz *J* = 1.8 Hz, 1H, PyH), 7.72 (dd, *J* = 5.9 Hz *J* < 1.8 Hz, 1H, PyH); IR (KBr): ν 3289 (broad, NH), 3027 (=CH-), 1782 (C=O, lactam and ester), 1741 (C=O, acetyl), 1683 and 1527 (C=O, amide), 1447 (CO_2-N), 1353 (C-N), 1227 (C-O, acetyl), 1133 (C=S) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 522 (3) [M+Na]$^+$, 500 (25) [M+H]$^+$, 331 (68), 237 (46), 154 (100) [NOBA],* 136 (73), 91 (55). (* defragmentation of NOBA matrix). HRMS (FAB, m/z): calculated for $C_{21}H_{20}O_4N_3S_2^+$: 442.0895 amu. Found: 442.0891 ± 0.0044 amu.

***N*1-(7*R*,7a*R*)-4-Bromo-3-[(*iso*propenyloxy)methyl]-6-oxo-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazin-7-yl-2-phenylacetamide (18)**

Following the general procedure (thiohydroxamic ester **17**, addition time: 15 min., bromotrichloromethane (15 ml) as trapping agent, flash chromatography (SiO_2, *n*-hexane / ethyl acetate 1:1) resulted, after crystallization (hexane / ethyl acetate), in **18** (0.276 g; 65%) as white needles.

Mp 121-122°C (dec.); $[\alpha]_D$ = +38° (c = 0.52; acetone); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 2.08 (s, 3H, C(O)CH_3), 3.34 and 3.54 (qAB, J_{AB} = 17.4 Hz, 2H, SCH_2), 3.86 (s, 2H, $PhCH_2$), 4.73 (s, 2H, CH_2OAc), 5.07 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 5.81 (dd, *J* = 4.9 Hz *J* = 9.0 Hz, 1H, NHC*H*CHS), 6.23 (d, *J* = 9.0 Hz, 1H, NH), 7.27-7.33 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 20.7 (CH_3), 27.9 (SCH_2), 43.2 ($PhCH_2$), 59.5 (CHNH), 60.7 (CHS), 65.4 (CH_2OAc), 112.0 (=CBr), 115.7 (=CCH_2OAc), 127.7, 129.2, 129.4 and 133.5 (PhC), 164.5 (C=O, lactam), 170.7 (OC(O)CH_3), 171.2 ($PhCH_2C$(O)); IR (KBr): ν 3264 (broad, NH), 1777 (C=O, lactam), 1741 (C=O, acetyl), 1658 and 1535 (C=O, amide), 1226 and 1059 (C-O, acetyl) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 447 (5) + 449 (5) [M+Na]$^+$, 425 (6) and 427 (7) [M+H]$^+$, 365 (48) and 367 (50) [M+H-$C_2H_4O_2$]$^+$, 337 (15) and 339 (15) [M+H-$C_2H_4O_2$-CO]$^+$, 219 (27) and 221 (27) [M+H-$C_2H_4O_2$-CO-$PhCH_2CO$]$^+$, 91 (100) [$PhCH_2^+$]; elem. anal.: calc. (found) for $C_{17}H_{17}O_4N_2SBr$: C: 48.01 (47.98), H: 4.03 (4.14), N: 6.59 (6.48).

4.6 References and notes

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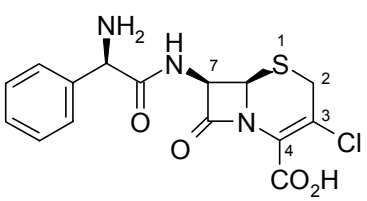
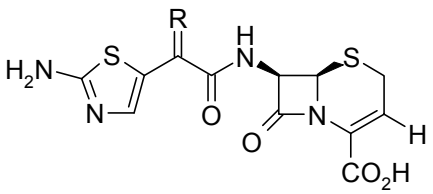
5 A NEW SYNTHESIS OF 3-CARBOXYCEPHEMS AND THEIR APPLICATION IN THE SYNTHESIS OF 3-NORCEHALOSPORINS

5.1 Introduction

Modifications of natural cephalosporins by chemical modification at C_3 have yielded biologically important derivatives.[1] Amongst others, 3-norcephalosporins bearing non-carbon atom substituents directly attached to the C_3 position are an interesting subclass of β-lactam antibiotics, particularly as potent orally active broad-spectrum drugs.[2]



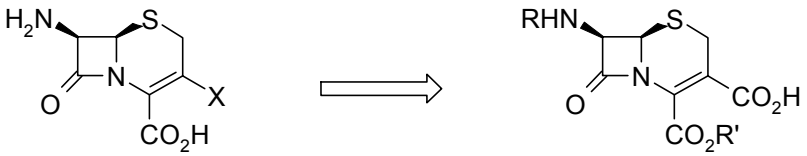
1 cefaclor



2 ceftibuten (R=CH(CH_2CO_2H))
3 ceftizoxime (R=N(OCH_3))

Figure 1.

Important examples are cefaclor (**1**), ceftibuten (**2**) (R=CH(CH_2CO_2H)) or ceftizoxime (**3**) (R=N(OCH_3)) (Figure 1). The most frequently encountered strategy to prepare these compounds starts with the fermentation products penicillin G or V and involves ozonolysis as the key step for the inevitable oxidative removal of one carbon atom.[3] Hitherto, no method for the preparation of 3-norcephalosporins has been described involving 3-carboxy-cephalosporins as the key-intermediates (Scheme 1).



X = H, Cl, Br, I

Scheme 1.

In chapter 4, the results of a synthetic study towards 3-norcephalosporins from 3-carboxycephems have been presented. Non-radical as well as radical approaches to accomplish a (halo)-decarboxylation reaction on the model compound 7-phenylacetyl-ADCA were investigated. Using Barton's radical decarboxylation reaction, a variety of 4-functionalized cephalosporins could be synthesized. Moderate to good yields were obtained for the introduction of hydrogen, chloride, bromide, iodide, and for the incorporation of selenium- and sulfur-containing groups.[4] In order to apply these findings to the 3-carboxycephalosporins, an improved synthesis of these important intermediates was needed, since these compounds are not readily available.

Although several syntheses of 3-carboxycephems have been reported, no convenient general procedure for both isomers regarding the double bond in the six-membered ring has been described so far. Spry *et al.*[5] and Peter *et al.*[6] were the first who synthesized the 3-carboxycephem derivatives from the corresponding 3-formylceph-2-ems in a sequence of reactions. In these approaches the conversion of the formyl group into the carboxyl group involved at least four separate steps. Also starting from cephalosporin thiolactones, a multi step procedure (bromination, hydrolysis, oxidation and opening of the dioxo thiophene ring) afforded the 3-carboxyceph-3-ems.[7] In addition, a few total syntheses have been reported.[8] Until now, no method for the direct oxidation of the 3-formylcephems to the 3-carboxycephems has been described. An economical and convenient synthesis of 3-carboxycephems with the double bond in the Δ^3- as well in the Δ^2-position will be reported in this chapter.[9]

Having secured the access to 3-carboxycephalosporins, the potential of the (halo)-decarboxylation reaction on these substrates was investigated. It will be shown that Barton's radical decarboxylation methodology allows the conversion of 3-carboxycephalosporins into 3-norcephalosporins with X = H, Cl, Br, and I.

5.2 Results and discussion

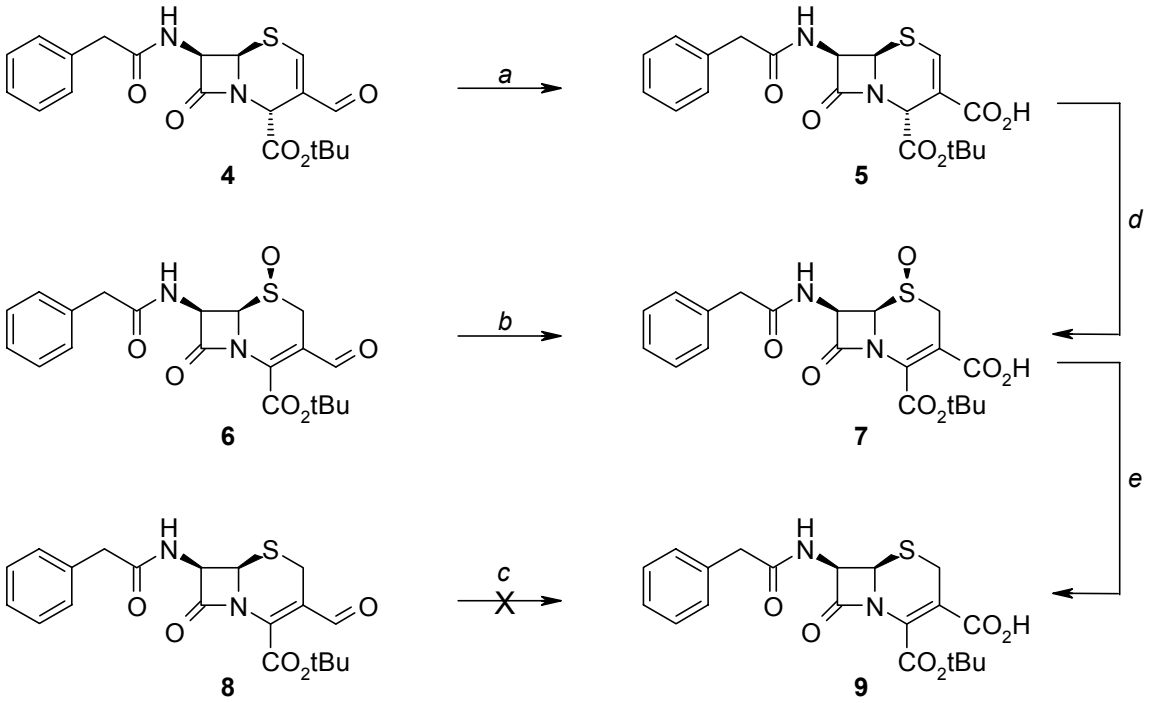
5.2.1 Synthesis of 3-carboxycephalosporins

In designing a new synthesis of 3-norcephalosporins, all possible isomers of 3-carboxycephalosporins with respect to the position of the double bond as well as the oxidation state of the sulfur atom had to be synthesized. It is well known that the chemical behavior, and therefore the stability, of the *β*-lactam nucleus strongly depends on the position of the double bond and the oxidation state of the sulfur atom. These subtle structural differences are possibly also of importance for the development of a new synthesis of 3-norcephalosporins.

The 3-formylcephalosporins[10] were chosen as the starting material. First 3-formylceph-3-em **4** was used in an oxidation reaction. Gratifyingly, oxidation of this formyl group in **4** to the carboxyl group was accomplished in a one step procedure by treatment with sodium chlorite ($NaClO_2$) in THF / phosphate buffer and cyclohexene as chlorine scavenger, thereby producing 3-carboxyceph-2-em **5** in an excellent yield of 93% (Scheme 2).

In principle, the synthesis of the corresponding 3-carboxyceph-3-em **7** (sulfoxide) can be realized in a similar manner. Again, formyl compound **6** was readily oxidized to the carboxylic acid by sodium chlorite in high yield. Disappointingly, when 3-formylceph-3-em **8** was used as the starting material, direct oxidation to the corresponding carboxyl group, using conditions similar to those used for the synthesis of 3-carboxyceph-2-em **5**, failed completely. Only severe decomposition had taken place as was deduced from TLC analysis. Probably opening of the *β*-lactam ring occurred by attack of a nucleophile (*e.g.* water) as was also observed by others.[11] The presence of an electron-withdrawing group on the C_3-position (in conjugation with the lactam moiety) also results in an enhanced chemical reactivity of the *β*-lactam C_6 carbonyl group.[6] When compared with the corresponding sulfoxide **6**, it should be mentioned that the sulfoxide function has a stabilizing effect

on the molecule.[12] Since this direct route to target compound **9** seems not possible, a detour *via* sulfoxide **7** was considered.



a) $NaClO_2$, cyclohexene, THF/phosphate buffer, 0°C, o/n 93%; b) $NaClO_2$, cyclohexene, THF/phosphate buffer, 0°C, o/n, 80%; c) $NaClO_2$, cyclohexene, THF/phosphate buffer, 0°C, 0%; d) m-CPBA, MeCN-CH_2Cl_2, 0°C, 4h, 78%; e) AcCl, $SnCl_2$, DMF, 0°C, 2h, 55%.

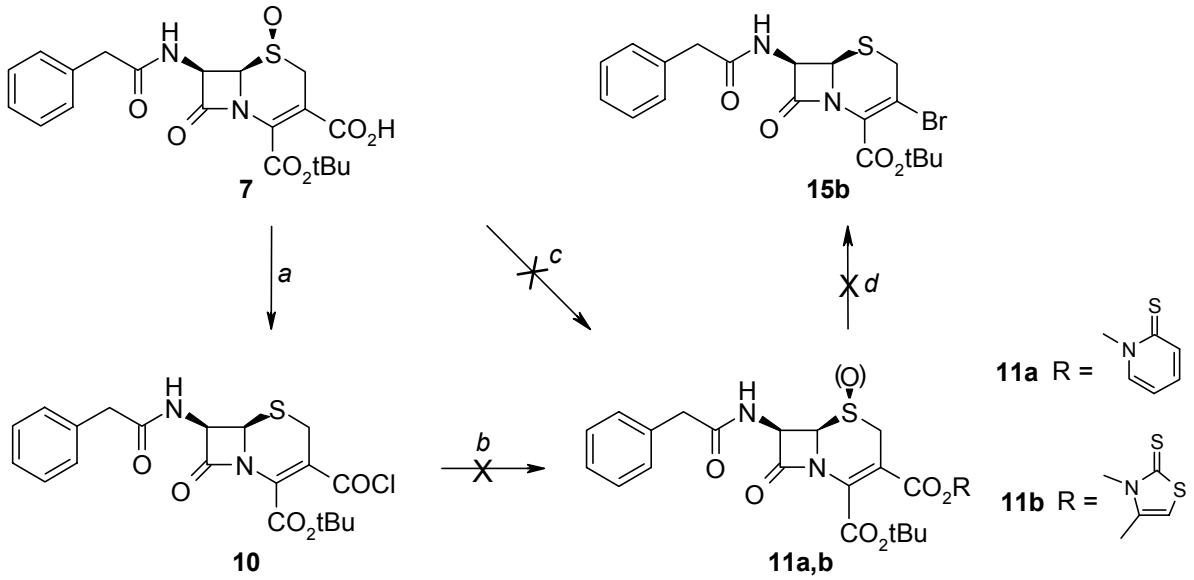
Scheme 2.

This sulfoxide could be synthesized *via* two methods: i. by oxidation of the corresponding Δ^2-isomer **5** with *meta*-chloroperbenzoic acid by adopting the procedure of Peter *et al*..[6] This oxidation gave compound **7** in 78% yield, ii. by oxidation of the formyl group in **6** (*vide supra*). The thus obtained sulfoxide **7** was then reduced to sulfide **9** by treatment with acetyl chloride in DMF in the presence of a catalytic amount of tin(II) chloride.[13] Thus, the abovementioned detour to target compound **9** *via* the sulfoxide route is indeed possible (Scheme 2). The chemistry shown in Scheme 2 clearly shows that subtle structural changes in the cephalosporin nucleus may change the course of reactions entirely.

5.2.2 Synthesis of 3-norcephalosporins using Barton's radical decarboxylation reactions

The crucial step in the synthesis of 3-norcephalsporins is the coupling of the 3-carboxycephalosporins with *N*-hydroxy-4-methyl-2-thiazolinethione. The question arises whether the same conditions can be used as for the synthesis of 4-norcephalosporins, which were described in the preceding chapter.[4],[10]

In a first attempt, the conversion of the carboxylic acid **7** to the corresponding acid chloride **10** was rather problematic, because above 0°C the formation of many by-products was observed (Scheme 3). It turned out that acid chloride **10** is only stable below 0°C. The quality of the acid chloride **10** was simply tested by its reaction with methanol which produces the corresponding methyl ester. At ambient temperature, this simple test only showed a mixture of products, which points to severe decomposition of compound **10**, and gave no methyl ester at all. It should be noted that during the formation of the acid chloride a reduction of the sulfoxide takes place, as was deduced from the spectra of the methyl ester.



a) Oxalylchloride, DMF (cat.), CH_2Cl_2, 0°C; b) 1 equiv. Barton reagent (hydroxy compound or Na-salt), CH_2Cl_2, r.t., overnight; c) DCC, Barton reagent (hydroxy compound), DMAP (cat.), CH_2Cl_2; d) $BrCCl_3$, reflux, 30% AIBN, 30'.

Scheme 3.

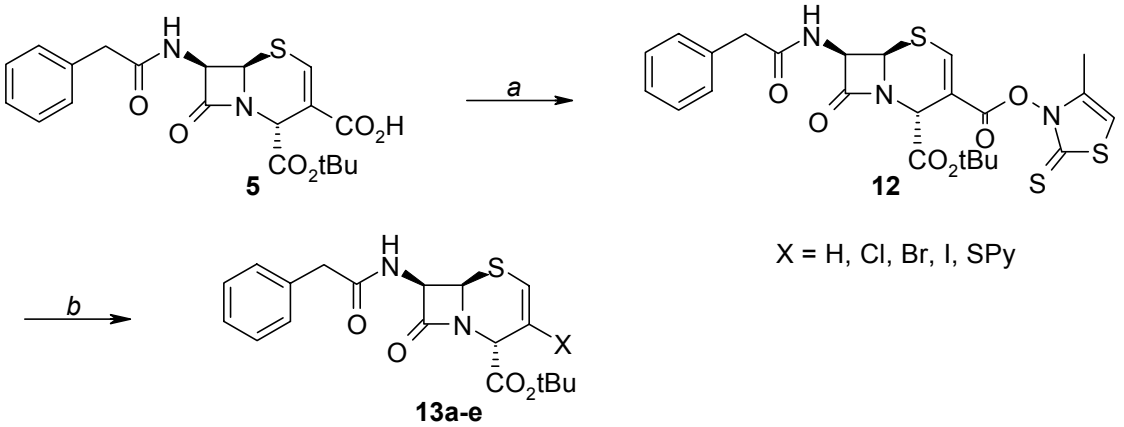
As an alternative, an *in situ* formation of Barton ester **11a** or **11b** to avoid decomposition of the acid chloride, was attempted (Scheme 3). Thus, after formation of acyl chloride **10**, the Barton reagent (*e.g.* *N*-hydroxy-4-methyl-2-thiazolinethione) was immediately added at 0°C. However, no ester **11a** or **11b** could be isolated. In a final attempt, acid chloride **10** was added to *N*-hydroxy-4-methyl-2-thiazolinethione in bromotrichloro methane at reflux under radical conditions, but again no Barton ester **11b** or desired decarboxylation product **15b** was observed. In view of these disappointing results with acid chloride **10**, other methods were considered.

As a first alternative, the coupling of *N*-hydroxy-4-methyl-2-thiazolinethione was tried with DCC (Scheme 3), but again the same serious problems were encountered. Apparently, the intermediate activated carboxylic acid derivative is, just as the acid chloride **10**, unstable under the chosen conditions and undergoes decomposition instead of coupling with the Barton reagent (OH compound). From the literature it became clear that oxalyl chloride and DCC can activate sulfoxides to give Pummerer-type of reactions.[14] From the viewpoint of electronic effects, a number of unsaturated electron withdrawing groups have been introduced at the 3-position, which are in conjugation with the Δ^3-double bond in the cephem ring. These groups participate in the delocalization of nitrogen's lone pair electrons thereby enhancing the reactivity (and therefore the instability) of the β-lactam amide bond.[15]

In view of the disappointing experience in the Δ^3-cephem derivative **7**, a substrate with the double bond in the Δ^2-position was investigated. Fortunately, 3-carboxyceph-2-em **5** appeared to be much more stable, since DCC coupling with *N*-hydroxy-4-methyl-2-thiazolinethione afforded Barton ester **12** in an excellent yield of 90% (Scheme 4). Purification of this ester by column chromatography confirmed the improved stability, which is probably attributable to the Δ^2-position of the double bond. Subsequently, the Barton bromo-decarboxylation reaction was studied. Thus, Barton ester **12** in dichloromethane was added under nitrogen to a solution of radical initiator AIBN in bromotrichloro methane at reflux, while irradiating with a tungsten lamp. This afforded bromide **13b** after purification in quite an acceptable yield of 69% (Table 1).

Applying the appropriate trapping agent, chloride and iodide could be introduced as well (Table 1). As expected, the yield of the chloride product **13a** is considerable lower than that of bromo compound **13b**. The trapping agent CCl_4 is much less able to release a chlorine radical than bromotrichloro methane a bromine radical. It

should be noted however, that in spite of the low yield, this introduction of a chloride at the C_3 position constitutes a new approach to the synthesis of the *β*-lactam core of cefaclor.



a) DCC, Barton reagent (OH compound), DMAP (cat.), -30°C → r.t., overnight, 90%; b) radical trap (solvent), reflux, 30% AIBN, 15-30', column chromatography.

Scheme 4.

Table 1: *Results of Barton's radical decarboxylation reactions with 3-carboxycephalosporin* ***5****.*

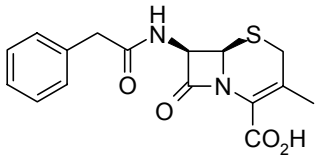
entry:	trapping agent:	product (X =):	nr:	yield (%):
1	CCl_4	Cl	**13a**	10
2	$CBrCl_3$	Br	**13b**	69
3	CHI_3	I	**13c**	28
4	CH_2I_2	SPy	**13d**	trace
5	*tert*-BuSH	H	**13e**	15
6	*n*-Bu_3SnH	H	**13e**	0

Iodide **13c** was obtained when iodoform was used as the trapping agent. The reaction conditions appeared to be very tricky, because prolonged reaction times lead to decomposition of the product. The solution slowly turned violet, due to the formation of several decomposition products. By monitoring the reaction very carefully, iodide **13c** was isolated in a maximum yield of 28%. With diiodomethane as the trapping agent,[16] no desired iodide **13c** was produced, but instead a small amount of sulfide **13d**. The structure of **13d** was deduced from its ^{1}H-NMR and mass spectrum. The formation of this sulfide **13d** is the result of trapping of the initial vinylic radical at C_3 by the Barton ester **12**. Such sulfides are usually encountered

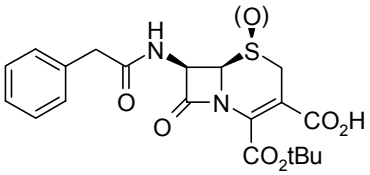
when no effective trapping agent is available (see discussion in Chapter 4, section 4.3).

The replacement of the C_3 carboxyl group by hydrogen with the aim to synthesize the building block for target compound **2** or **3** was not as straightforward as expected. Initially, *tert*-butyl mercaptane as the trapping agent[17] seemed unsuccessful. Therefore, another trapping agent was tried, *viz*. tributyltin hydride, which has been used for decarboxylations before.[18] Unfortunately, according to a TLC analysis, only very polar products were formed. Detailed reconsidering the reaction conditions (especially shortening the reaction time), for *tert*-butyl mercaptane as the trapping agent, afforded the parent cephalosporin skeleton **13e** in a modest yield of 15%.

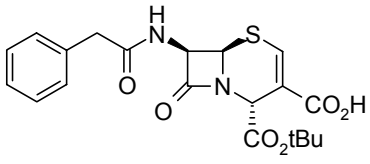
Comparison of the results obtained in this chapter with those for the Barton (halo)-decarboxylation of the C_4-carboxyl group in 7-phenylacetyl-ADCA reveals that the radical decarboxylation proceeded more smoothly in the case of the C_4-carboxyl compound (see formulas below).



model compound
(see Chapter 4)

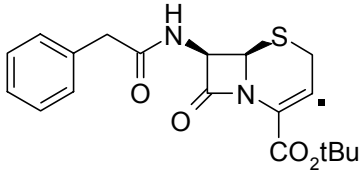


Δ^3-3-carboxycephem system



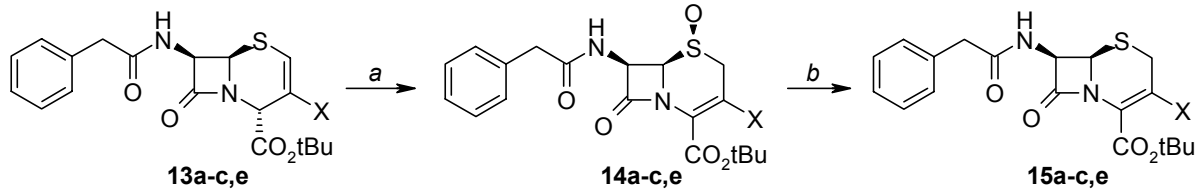
Δ^2-3-carboxycephem system

Apparently, this difference in behavior between the Barton decarboxylation reaction at C_3 an C_4 must be due to the different nature of the respective intermediate vinylic radicals. When such a radical is generated from Δ^3-3-carboxycephem **9** (see formula below), the presence of the electron-withdrawing ester group at C_4 and a double bond in Δ^3-position, cause a destabilizing effect on the β-lactam ring, which results in untimely decomposition reactions.[15]



vinylic radical generated
from Δ^3 3-carboxycephem **9**

When the double bond is present in the Δ^2-position, this destabilizing effect *via* conjugation with the *β*-lactam amide bond is not possible and therefore the vinylic radical generated from the Δ^2-3-carboxycephem system show a better trapping behavior in the Barton reaction. In the model compound, the vinylic radical at C_4 does not suffer from destabilizing effects by a substituent at C_3, hence better decarboxylation results are to be expected. From the discussion above, it may be concluded that for the synthesis of 3-norcephalosporins the Δ^2-3-carboxycephalosporins are the substrates of choice when the Barton radical decarboxylation is used as the key reaction. However, for antibacterial activity, it is necessary to convert the double bond to the Δ^3-position. In *β*-lactam chemistry this conversion is a standard procedure and involves oxidation of the sulfide to the corresponding sulfoxide (*e.g.* with *m*-CPBA).[13] During this oxidation the double bond migrates to the Δ^3-position. Subsequent reduction back to the corresponding sulfide the double bond is retained in the Δ^3-position (Scheme 5).



a) m-CPBA, CH_2Cl_2, 0°C, 1.5h; b) TFAA, sodium iodide, acetone, 0°C, 1-2h.

Scheme 5.

Table 2: *Results of the oxidation - reduction sequence to obtain the corresponding Δ^3-isomers.*

entry:	substrate (X =):		sulfoxide (%):		sulfide (%):	
1	**13a**	Cl	**14a**	(92)	**15a**	(69)
2	**13b**	Br	**14b**	(92)	**15b**	(50)
3	**13c**	I	**14c**	(0)[a]	**15c**	-[b]
4	**13e**	H	**14e**	(61)	**15e**	(72)

[a] decomposition

[b] not investigated

The results of the conversion of the Δ^2-compounds *via* the corresponding sulfoxides into the Δ^3-sulfide analogs are collected in Table 2. The data in the table show that conversion to the sulfoxides is facile and high yielding for all compounds except for iodide **13d**. A possible explanation could be the formation of hyper valent iodine compounds upon treatment with *m*-CPBA. The use of a milder reagent for the

oxidation (*e.g.* dimethyldioxirane) could possibly circumvent this problem with iodide **13d**.

5.3 Concluding remarks

A convenient synthesis of some 3-carboxycephems, namely for 3-carboxyceph-2-em **5** and 3-carboxyceph-3-em sulfoxide **7**, and the corresponding sulfide **9**, starting from the 3-formylcephalosporins was developed. These 3-carboxy derivatives precursors for the synthesis of 3-norcephalosporins. Using the Barton radical decarboxylation reaction, hydrogen, chloride, and iodide could be introduced in low to modest yields, while bromide was incorporated in an excellent yield. A remarkable difference was encountered in the reactivity and stability of the Δ^2- and Δ^3-isomers. The most rewarding results were obtained for substrate **5** with the double bond in the Δ^2-position. The (halo)-decarboxylation reactions represent the use of radical chemistry in the synthesis of 3-norcephalosporins for the first time.

From an industrial point of view, at this stage, the Barton methodology is less attractive for the synthesis of C_3-unsubstituted and 3-chloro-substituted cephems, because of the low yields of the (halo)-decarboxylation reactions. It should be noted, however, that the Barton decarboxylation reaction on itself would not be the bottleneck in an industrial process, as this reaction has already been conducted on a large scale in industry in the area of steroid chemistry.[19]

5.4 Experimental part

General remarks

100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer and 300 MHz ^{1}H-NMR spectra and all ^{13}C-NMR spectra were recorded on a Bruker AC 300 using Me_4Si as internal standard. All coupling constants are given as ^{3}J in Hz, unless indicated otherwise. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FTS-25 instrument. For mass spectra a double focusing VG7070E mass spectrometer was used. Elemental analyses were conducted on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. For the determination of optical rotations a Perkin-Elmer 241 polarimeter was used. Solvents were dried using the following methods: dichloromethane was distilled from P_2O_5; ethyl acetate was distilled from K_2CO_3; diethyl ether was distilled from NaH; hexane and heptane were distilled from CaH_2; tetrahydrofuran was distilled from sodium just before use. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on a Merck precoated

silica gel 60 F254 plates (0.25 mm). Spots were visualized with UV or using a molybdate spray. Flash chromatography was carried out at a pressure of *ca*. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was performed with ACROS silicagel (0.035-0.070 mm; pore diameter ca. 6 nm).
Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada).

(4*S*,7*R*,7a*R*)-4-(*tert*-Butoxycarbonyl)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-3-carboxylic acid (5)

Aldehyde **4** (0.8 g; 1.99 mmol) was dissolved in THF (28 ml) and cyclohexene (8 ml) was added. After cooling to 0°C a mixture of KH_2PO_4 (1.5 g) and $NaClO_2$ (1.2 g) dissolved in water (28 ml) was added. The reaction mixture was allowed to warm up to room temperature slowly and then stirred overnight. The reaction mixture was then acidified with 2N HCl and THF was removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (3x75 ml). The combined organic layers were washed with brine (1x100 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was washed with ether to obtain acid **5** (770 mg; 93%). An analytically pure sample was obtained by column chromatography (SiO_2, ethyl acetate / hexane 1:1).
Mp 178-180°C (dec.); $[\alpha]_D$ = +535° (c = 1.0; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.44 (s, 9H, $C(CH_3)_3$), 3.64 (s, 2H, $PhCH_2$), 5.15 (d, *J* = 3.9 Hz, 1H, NHCHC*H*S), 5.21 (s, 1H, C*H*$CO_2{}^t$Bu), 5.55 (dd, *J* = 3.9 Hz *J* = 7.8 Hz, 1H, NHC*H*CHS), 6.61 (d, *J* = 7.8 Hz, 1H, NH), 7.25-7.35 (m, 5H, PhH), 7.74 (s, SCH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 49.8 ($CHCO_2{}^t$Bu) 53.9 (CHNH), 60.4 (CHS), 83.7 ($C(CH_3)_3$), 116.1 (=CCO_2H), 127.7, 129.1, 129.4 and 133.5 (PhC), 138.0 (SCH) 163.9 (C=O, lactam), 165.7 ($CHCO_2{}^t$Bu), 167.5 (CO_2H), 171.5 ($PhCH_2C$(O)); IR (KBr): ν 3326 (broad, NH), 1805 (C=O, lactam), 1736 (C=O, ester), 1678 and 1537 (C=O, amide), 1640 (C=O, acid), 1389 (C-N) 1162 (C-O, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 441 (16) $[M+Na]^+$, 419 (7) $[M+H]^+$, 385 (8) $[M+Na-C_4H_8]^+$, 363 (33) $[M+H-C_4H_8]^+$, 317 (5) $[M+H-C_4H_8-CO_2]^+$, 178 (100); elem. anal.: calc. (found) for $C_{20}H_{22}O_6N_2S$: C: 57.40 (57.56), H: 5.30 (5.35), N: 6.69 (6.65).

(7*R*,7a*R*)-4-(*tert*-Butoxycarbonyl)-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-3-carboxylic acid (7)

This compound was prepared from aldehyde **6** (0.777 g; 1.86 mmol) in the same way as described for the synthesis of 3-carboxyceph-2-em **5**. Yield after purification (0.645 g; 80%).

Alternative approach

3-Carboxyceph-2-em **5** (0.320 g; 0.77 mmol) was treated with 1.5 equiv. of pre-dried *m*-CPBA in a mixture of dichloromethane / acetonitrile (1:1) at 0°C for 4h. After completion, a saturated solution of $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (2x50 ml). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product thus obtained was purified by stirring in diethyl ether to remove *m*-chlorobenzoic acid affording **7** as a white amorphous solid (0.260 g; 78%).
Mp 163-165°C (dec.); $[\alpha]_D$ = 9.80° (c = 0.49; acetone); ^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm) = 1.52 (s, 9H, $C(CH_3)_3$), 3.44 (dd, *J* = 18.1 Hz ^4J = 1.8 Hz, 1H, SCH_2), 3.63 (qAB, J_{AB} = 14.6 Hz, 2H, $PhCH_2$), 4.26 (d, *J* = 18.1 Hz, 1H, SCH_2), 4.89 (dd, *J* = 5.1 Hz ^4J = 1.6 Hz, 1H, NHCHC*H*S), 6.12 (d, *J* = 5.1 Hz, 1H, NHC*H*CHS), 7.25-7.40 (m, 5H, PhH); ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.1

(SCH_2), 44.8 ($PhCH_2$), 60.3 (CHNH), 68.1 (CHS), 83.9 ($C(CH_3)_3$), 119.7 (=CCO_2H), 127.6, 129.3, 130.1 and 136.4 (PhC), 136.6 (=$CCO_2{}^tBu$), 161.1 ($CO_2{}^tBu$), 165.5 (C=O, lactam), 167.9 (CO_2H), 172.6 ($PhCH_2C(O)$); IR (KBr): ν 3332 (broad, NH), 2980 and 2927 (COO-H), 1793 (C=O, lactam), 1729 (C=O, ester), 1689 (C=O, acid), 1657 and 1523 (C=O, amide) 1380 (C-N), 1215 (C-O, ester), 1039 (S=O) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 457 (4) $[M+Na]^+$, 434 (4) $[M^+]$, 393 (12) $[M+Na-C_4H_8]^+$, 379 (11) $[M+H-C_4H_8]^+$, 322 (12), 154 (100) $[NOBA]^*$, 57 (74) $[C_4H_9^+]$; HRMS (FAB, m/z): calculated for $C_{20}H_{22}O_7N_2SNa^+$: 457.1045 amu. Found: 457.0984 ± 0.0046 amu.

(7*R*,7a*R*)-4-(*tert*-Butoxycarbonyl)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-3-carboxylic acid (9)

A solution of sulfoxide **7** (0.350 g; 0.73 mmol) in dry DMF (3 ml) was treated with tin(II) chloride (0.481 g; 2.75 mmol) and an excess of acetyl chloride (1.5 ml) at 0°C for 2h. After removal of excess acetyl chloride (*in vacuo*) ethyl acetate and water were added. Extraction with ethyl acetate (2x50 ml), drying ($MgSO_4$) and concentration *in vacuo* afforded the crude sulfide in nearly quantitative yield. Purification by column chromatography (SiO_2, ethyl acetate / acetone 1:1) gave sulfide **9** (0.185 g; 55%) as a white solid. An analytically pure sample was obtained by recrystallization from diethyl ether.

Mp 165-167 °C (dec.); $[\alpha]_D$ = -58.8° (c = 0.32; acetone); ^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm) = 1.51 (s, 9H, $C(CH_3)_3$), 3.57 and 3.86 (qAB, J_{AB} = 17.8 Hz, 2H, SCH_2), 3.67 and 3.68 (qAB, J_{AB} = 14.3 Hz, 2H, $PhCH_2$), 5.17 (d, *J* = 5.1 Hz, 1H, NHCHC*H*S), 5.90 (dd, *J* = 5.1 Hz *J* = 8.9 Hz, 1H, NHC*H*CHS), 7.24-7.38 (m, 5H, PhH), 8.17 (d, *J* = 8.9 Hz, 1H, NH); ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm) = 25.0 (SCH_2), 27.8 ($C(CH_3)_3$), 43.0 ($PhCH_2$), 60.0 and 60.8 (CHNH and CHS), 83.6 ($C(CH_3)_3$), 110.7 (=CCO_2H), 127.5, 129.1, 130.0 and 136.4 (PhC), 136.6 (=$CCO_2{}^tBu$), 161.7 ($CO_2{}^tBu$), 165.3 (C=O, lactam), 166.3 (CO_2H), 171.6 ($PhCH_2C(O)$); IR (KBr): ν 3298 (broad, NH), 2978 (COO-H), 1795 (C=O, lactam), 1730 (C=O, ester), 1716 (C=O, acid), 1684 and 1523 (C=O, amide) 1369 (C-N), 1155 (C-O, ester) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 441 (14) $[M+Na]^+$, 419 (16) $[M+H]^+$, 363 (53) $[M+H-C_4H_8]^+$, 176 (100); elem. anal.: calc. (found) for $C_{20}H_{22}O_6N_2S$: C: 57.40 (57.29), H: 5.30 (5.30), N: 6.69 (6.54).

4-(*tert*-Butyl) 3-(4-methyl-2-thioxo-2,3-dihydro-1,3-thiazol-3-yl) (4*S*,7*R*,7a*R*)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-3,4-dicarboxylate (12)

To a cooled (-30°C) and stirred solution of 3-carboxyceph-2-em **5** (0.150 g; 1.07 mmol) in dichloromethane (15 ml), DCC (0.331 g; 1.61 mmol), Barton reagent (0.236 g; 1.61 mmol) and DMAP as a catalyst were added, under a nitrogen atmosphere. After stirring for 1h at -30°C, the reaction mixture was allowed to warm to room temperature and stirred for another 15h. After concentration *in vacuo*, ethyl acetate was added and the DCU, formed during the reaction, was removed by filtration over hyflo. The filtrate was extracted with 5% HCl solution. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified using column chromatography (SiO_2, ethyl acetate / heptane 1:1) affording **12** (0.530 g; 90%) as a white solid.

Mp 120-122°C (dec.); $[\alpha]_D$ = +422.4° (c = 0.50; acetone); ^{1}H-NMR (400 MHz, 60°C, acetone-d_6) δ (ppm) = 1.46 (s, 9H, $C(CH_3)_3$), 3.64 (s, 2H, $PhCH_2$), 5.21 (bs, 1H, NHCHC*H*S), 5.34 (s, 1H, C*H*$CO_2{}^tBu$), 5.56 (dd, *J* = 3.9 Hz *J* = 7.5 Hz, 1H, NHC*H*CHS), 6.19 (s, 1H, MeC=C*H*S), 6.23 (bs, 1H, NH), 7.25-7.38 (m, 5H, PhH), 8.20 (bs, 1H, SCH=); IR (KBr): ν 3283 (broad, NH), 1775 (C=O, lactam), 1734 (C=O, ester), 1651 and 1522 (C=O, amide), 1340 (C-N), 1154 (C-O, ester) cm^{-1}; MS (FAB^+, NOBA): *m/z* (%) = 570 (10)

$[M+Na]^+$, 548 (73) $[M+H]^+$, 492 (10) $[M+H\text{-}C_4H_8]^+$, 419 (6) $[M+H\text{-}C_4H_4NS_2]^+$, 346 (25), 290 (23), 225 (100), 176 (29), 148 (84); HRMS (FAB, m/z): calculated for $C_{24}H_{25}O_6N_3S_3^+$ $[M+H]^+$: 548.0984 amu. Found: 548.1007 ± 0.0055 amu.

***tert*-Butyl (4*R*,7*R*,7a*R*)-3-chloro-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13a)**

Thiohydroxamic ester **12** (0.130 g; 0.237 mmol) in chlorobenzene (5 ml) was added, under nitrogen, to a boiling mixture of chlorobenzene and carbon tetrachloride (3:2) containing AIBN (50 mg). During addition the reaction mixture was irradiated with a tungsten lamp (250 W). After completion (30 min.), all solvents were removed *in vacuo*. The crude product was purified *via* column chromatography (SiO_2, CH_2Cl_2 / acetone 19:1) yielding **13a** (9.6 mg; 10%) as a white solid. An analytical sample was obtained by recrystallization from heptane / ethyl acetate.

Mp 107-108°C (dec.); $[\alpha]_D$ = +492° (c = 0.50; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.49 (s, 9H, $C(CH_3)_3$), 3.63 and 3.65 (qAB, J_{AB} = 16.1 Hz, 2H, $PhCH_2$), 4.75 (d, ^{4}J = 1.6 Hz, 1H, $CHCO_2{}^tBu$), 5.29 (d, J = 4.0 Hz, 1H, NHCHCHS), 5.63 (dd, J = 4.0 Hz J = 8.7 Hz, 1H, NHCHCHS), 6.28 (d, ^{4}J = 1.6 Hz, 1H, SCH=), 6.30 (d, J = 8.7 Hz, 1H, NH), 7.25-7.40 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.3 ($PhCH_2$), 53.1 ($CHCO_2{}^tBu$)*, 54.5 (CHNH)*, 60.0 (CHS), 84.3 ($C(CH_3)_3$), 114.5 (=CCl), 116.9 (SCH=), 127.7, 129.2, 129.5 and 133.5 (PhC), 164.2 (C=O, lactam), 165.1 ($CHCO_2{}^tBu$), 171.0 ($PhCH_2C(O)$) (*: signals may have interchanged); IR (KBr): ν 3311 (broad, NH), 1775 (C=O, lactam), 1728 (C=O, ester), 1658 and 1526 (C=O, amide), 1333 (C-N), 1157 (O-C, ester) cm^{-1}; MS (FAB^+, NOBA): m/z (%) = 431 (14) $[M+Na]^+$, 409 (16) $[M+H]^+$, 353 (7) $[M+H\text{-}C_4H_8]$, 234 (17), 176 (100), 91 (22) $[PhCH_2^+]$, 57 (18) $[C_4H_9^+]$; HRMS (CI^+, m/z): calculated for $C_{19}H_{21}O_4N_2SCl$ $[M+H]^+$: 409.09888 amu. Found: 409.09852 ± 0.00123 amu.

***tert*-Butyl (4*R*,7*R*,7a*R*)-3-bromo-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13b)**

Barton ester **12** (0.340 g; 0.622 mmol) dissolved in a mixture of bromotrichloromethane and dichloromethane (10 ml) was added, under nitrogen, to a solution of AIBN (100 mg) in bromotrichloromethane at reflux conditions while irradiated with a 250 W tungsten lamp. When TLC analysis (hexane / ethyl acetate 1:1) showed completion of the reaction, the reaction mixture was concentrated to dryness. The crude product was purified over silicagel (heptane / ethyl acetate 1:1) to give bromine **13b** as a white solid (0.196 g, 69%) that was recrystallized from heptane / ethyl acetate.

Mp 149-151°C (dec.); $[\alpha]_D$ = +502° (c = 0.155; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.50 (s, 9H, $C(CH_3)_3$), 3.63 and 3.66 (qAB, J_{AB} = 16.2 Hz, 2H, $PhCH_2$), 4.81 (d, ^4J = 1.7 Hz, 1H, $CHCO_2{}^tBu$), 5.32 (d, *J* = 4.0 Hz, 1H, NHCHC*H*S), 5.63 (dd, *J* = 4.0 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 6.21 (d, *J* = 8.7 Hz, 1H, NH), 6.49 (d, ^4J = 1.7 Hz, 1H, SCH=), 7.25-7.41 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.3 ($PhCH_2$), 52.9 ($CHCO_2{}^tBu$)*, 55.4 (CHNH)*, 60.3 (CHS), 84.3 ($C(CH_3)_3$), 101.5 (=CBr), 119.6 (SCH=), 127.7, 129.2, 129.5 and 133.5 (PhC), 164.0 (C=O, lactam), 165.2 ($CHCO_2{}^tBu$), 171.0 ($PhCH_2C(O)$) (*: signals may have interchanged); IR (KBr): ν 3296 (broad, NH), 1780 (C=O, lactam), 1738 (C=O, ester), 1669 and 1540 (C=O, amide), 1370 (C-N), 1151 (O-C, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 453 (3) and 455 (3) $[M+H]^+$, 425 (5) and 427 (5) $[M+H\text{-}CO]^+$, 397 (5) and 399 (5) $[M+H\text{-}C_4H_8]^+$, 351 (3) and 353 (4) $[M+H\text{-}C_4H_8\text{-}CO_2]^+$, 278 (24) and 280 (24) $[M+H\text{-}C_4H_8\text{-}C_7H_7\text{-}CO]^+$, 222 (47) and 224 (48), 176 (100), 91 (58) $[PhCH_2^+]$, 57 (66) $[C_4H_9^+]$; HRMS (CI^+, m/z): calculated for $C_{19}H_{21}O_4N_2SBr$ $[M+H]^+$: 453.04838 amu. Found: 453.04730 ± 0.00136 amu.

tert-Butyl (4*R*,7*R*,7a*R*)-3-iodo-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13c)

Barton ester **12** (0.100 g; 0.182 mmol) and AIBN (0.20 g) in dichloromethane were added, under nitrogen, to a solution of iodoform (0.80 g, 2.0 mmol) in toluene (10 ml) at reflux while irradiating with a tungsten lamp (250 W). The reaction was carefully monitored by TLC and after completion the solvents were removed in vacuo. Purification by column chromatography (SiO_2, CH_2Cl_2 / acetone 19:1) gave **13c** (0.026 g; 28%) as yellowish white plates. The compound was light sensitive (color turned brown upon standing).

Mp 55-57°C (dec.); ^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 1.52 (s, 9H, $C(CH_3)_3$), 3.63 (s, 2H, $PhCH_2$), 4.82 (d, ^4J = 1.7 Hz, 1H, C*H*$CO_2{}^t$Bu), 5.36 (d, *J* = 4.0 Hz, 1H, NHCHC*H*S), 5.60 (dd, *J* = 4.0 Hz *J* = 8.6 Hz, 1H, NHC*H*CHS), 6.33 (d, *J* = 8.6 Hz, 1H, NH), 6.72 (d, ^4J = 1.7 Hz, 1H, SCH=), 7.27-7.33 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.9 ($C(CH_3)_3$), 43.3 ($PhCH_2$), 52.5 ($CHCO_2{}^t$Bu)*, 57.2 (CHNH)*, 60.7 (CHS), 70.7 (=CI), 84.4 ($C(CH_3)_3$), 125.7 (SCH=), 127.8, 129.2, 129.5 and 133.6 (PhC), 163.8 (C=O, lactam), 165.3 ($CHCO_2{}^t$Bu), 171.1 ($PhCH_2C$(O)) (*: signals may have interchanged); IR (KBr): ν 3043 (broad, NH), 1780 (C=O, lactam), 1736 (C=O, ester), 1662 and 1541 (C=O, amide), 1369 (C-N), 1148 (O-C, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 501 (2) [M+H]$^+$, 445 (4) [M+H-C_4H_8]$^+$, 326 (9), 270 (21), 234 (7), 176 (100), 57 (10) [$C_4H_9^+$]; HRMS (CI$^+$, m/z): calculated for $C_{19}H_{21}O_4N_2SI$ [M+H]$^+$: 501.03450 amu. Found: 501.03328 ± 0.00150 amu.

tert-Butyl (7*R*,7a*R*)-3-[(4-methyl-1,3-thiazol-2-yl)sulfanyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13d)

The reaction was carried out as described for compound 13c, using diiodomethane as the trapping agent. Only a trace amount of sulfide **13d** was isolated.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.45 (s, 9H, $C(CH_3)_3$), 2.40 (s, 3H, CH_3), 3.67 (s, 2H, $PhCH_2$), 5.23 (d, *J* = 3.9 Hz, 1H, NHCHC*H*S), 5.38 (d, *J* = 1.1 Hz, 1H, C=C*H*$CO_2{}^t$Bu), 5.60 (dd, *J* = 3.9 Hz *J* = 7.7 Hz, 1H, NHC*H*CHS), 6.12 (d, *J* = 7.7 Hz, 1H, NH), 7.28-7.38 (m, 6H, PhH and SC*H*=CCH_3), 6.24 (d, *J* = 10.4 Hz *J* = 1.1 Hz, 1H, SC*H*=C); MS (FAB$^+$, NOBA): *m/z* (%) = 504 (20) [M+H]$^+$, 448 (<1) [M+H-C_4H_8]$^+$, 345 (41), 288 (80), 176 (72), 154 (100) [NOBA]*, 91 (54) [$PhCH_2^+$], 57 (43) [$C_4H_9^+$] (* defragmentation of NOBA matrix).

tert-Butyl (4*R*,7*R*,7a*R*)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13e)

A solution of thiohydroxamic ester **12** (0.300 g; 0.548 mmol) and AIBN (100 mg) in dichloromethane (5 ml) was added dropwise, under an inert atmosphere, to a solution of *tert*-butyl mercaptane (1 ml) in toluene at reflux, while irradiating with a tungsten lamp (250 W). After complete conversion, the reaction mixture was concentrated *in vacuo* to remove all solvents and the crude product was purified over silica gel (heptane / ethyl acetate 1:1), giving **13e** (0.030 g; 15%) as a white solid material. ^{1}H-NMR showed an inseparable mixture of Δ^2- / Δ^3-isomers (1:1).

Δ^3-isomer

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.51 (s, 9H, $C(CH_3)_3$), 3.38 and 3.50 (qAB, J_{AB} = 19.1 Hz *J* = 6.2 Hz *J* = 2.5 Hz, 2H, SCH_2), 3.62 (s, 2H, $PhCH_2$), 4.88 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.88 (dd, *J* = 5.0 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.38 (dd, *J* = 6.1 Hz *J* = 2.4 Hz, 1H, =CH), 6.93 (d, *J* = 9.2 Hz, 1H, NH), 7.23-7.36 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 24.0 (SCH_2), 27.8 ($C(CH_3)_3$), 42.9

($PhCH_2$), 56.8 (HNH), 59.3 (CHS), 82.8 ($C(CH_3)_3$), 118.5 (=CH), 129.1 (=$CCO_2{}^tBu$), 127.2, 128.7, 129.1 and 134.1 (PhC), 160.4 ($CO_2{}^tBu$), 164.7 (C=O, lactam), 171.3 ($PhCH_2C(O)$).

Δ^2-isomer

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.46 (s, 9H, $C(CH_3)_3$), 3.62 (s, 2H, $PhCH_2$), 4.75 (dd, *J* = 2.4 Hz *J* = 4.3 Hz, 1H, C=C*H*$CO_2{}^tBu$), 5.15 (d, *J* = 4.0 Hz, 1H, NHCHC*H*S), 5.67 (dd, *J* = 4.0 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 5.76 (dd, *J* = 10.4 Hz *J* = 4.3 Hz, 1H, SCH=C*H*), 6.24 (dd, *J* = 10.4 Hz *J* = 2.4 Hz, 1H, SC*H*=CH), 6.65 (d, *J* = 8.7 Hz, 1H, NH), 7.23-7.36 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 50.0 (CHNH)*, 53.5 ($CHCO_2{}^tBu$)*, 60.5 (CHS), 83.3 ($C(CH_3)_3$), 113.5 (SCH=*C*H), 119.7 (SCH=), 127.3, 128.8, 129.2 and 133.8 (PhC), 160.4 (C=O, lactam), 166.3 ($CHCO_2{}^tBu$), 171.1 ($PhCH_2C(O)$) (*: signals may have interchanged); IR (KBr): ν 3308 (broad, NH), 1770 (broad, C=O, lactam), 1716 (C=O, ester), 1681, 1661 and 1539 (C=O, amide), 1367 and 1406 (C-N), 1155 (C-O, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 374 (2) [M^+], 319 (15) [$M+H-C_4H_8]^+$, 176 (100), 144 (61), 91 (84) [$PhCH_2^+$], 57 (79) [$C_4H_9^+$]; HRMS (CI^+, m/z): calculated for $C_{19}H_{22}O_4N_2S$ [$M+H]^+$: 375.13785 amu. Found: 375.13701 ± 0.00112 amu.

***tert*-Butyl (7*R*,7*aR*)-3-chloro-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (14a)**

To a solution of sulfide **13a** (0.300 g; 0.73 mmol) in dichloromethane (10 ml), *m*-CPBA (0.133 g; 0.77 mmol) was added at 0°C. After stirring for 1h at 0°C, the reaction mixture was concentrated *in vacuo*. Silica gel chromatography (heptane / ethyl acetate 2:3) afforded sulfoxide **14a** (0.287 g; 92%) as a white solid.

Mp 173-175°C (dec.); $[\alpha]_D$ = +53.1° (c = 0.52; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.54 (s, 9H, $C(CH_3)_3$), 3.51 and 3.81 (qAB, J_{AB} = 18.5 Hz *J* = 1.6 Hz, 2H, SCH_2), 3.61 and 3.62 (qAB, J_{AB} = 15.8 Hz, 2H, $PhCH_2$), 4.53 (dd, *J* = 4.9 Hz *J* < 1.5 Hz, 1H, NHCHC*H*S), 5.98 (dd, *J* = 4.9 Hz *J* = 9.7 Hz, 1H, NHC*H*CHS), 7.08 (d, *J* = 9.7 Hz, 1H, NH), 7.24-7.34 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 42.9 ($PhCH_2$), 50.4 (SCH_2), 58.9 (CHNH), 67.0 (CHS), 84.6 ($C(CH_3)_3$), 117.7 (=CCl), 126.0 (=$CCO_2{}^tBu$), 127.4, 128.9, 129.3 and 133.9 (PhC), 158.2 ($CO_2{}^tBu$), 163.3 (C=O, lactam), 171.7 ($PhCH_2C(O)$); IR (KBr): ν 3282 (broad, NH), 1786 (C=O, lactam), 1726 (C=O, ester), 1651 and 1533 (C=O, amide), 1369 (C-N), 1156 (C-O, ester), 1040 (S=O) cm^{-1}; MS (CI^+): *m/z* (%) = 369 (3) [$M+H-C_4H_8]^+$, 324 (5) [$M+H-C_4H_8-CO_2]^+$, 276 (11), 235 (19), 219 (17), 203 (54), 91 (100) [$PhCH_2^+$], 57 (72) [$C_4H_9^+$]; HRMS (CI^+, m/z): calculated for $C_{19}H_{21}O_5N_2SCl$ [$M+H]^+$: 425.09380 amu. Found: 425.09365 ± 0.00128 amu.

***tert*-Butyl (7*R*,7a*R*)-3-bromo-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (14b)**

Sulfide **13b** (0.196 g; 0.43 mmol) was oxidized following the procedure described for chloride **13a**. Column chromatography (heptane / ethyl acetate 2:3) afforded **14b** (0.187 g; 92%) as a white crystalline solid.

Mp 210°C (dec.); $[\alpha]_D$ = +32.4° (c = 0.50; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.55 (s, 9H, $C(CH_3)_3$), 3.57 and 3.98 (qAB, J_{AB} = 18.6 Hz *J* = 1.5 Hz, 2H, SCH_2), 3.60 and 3.63 (qAB, J_{AB} = 15.5 Hz, 2H, $PhCH_2$), 4.52 (dd, *J* = 4.7 Hz *J* < 1.5 Hz, 1H, NHCHC*H*S), 6.00 (dd, *J* = 4.7 Hz *J* = 9.8 Hz, 1H, NHC*H*CHS), 6.90 (d, *J* = 9.8 Hz, 1H, NH), 7.25-7.40 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 52.1 (SCH_2), 59.3 (CHNH), 66.9 (CHS), 84.8 ($C(CH_3)_3$), 105.0 (=CBr), 127.7 (=$CCO_2{}^tBu$), 127.5, 128.9, 129.4 and 133.8 (PhC), 158.8 ($CO_2{}^tBu$), 163.0 (C=O, lactam), 171.4

($PhCH_2C(O)$); IR (KBr): ν 3280 (broad, NH), 1784 (C=O, lactam), 1726 (C=O, ester), 1651 and 1533 (C=O, amide), 1368 (C-N), 1155 (C-O, ester), 1040 (S=O) cm^{-1}; MS (CI^+): *m/z* (%) = 413 (1) and 415 (1) $[M+H-C_4H_8]^+$, 369 (1) and 371 (1) $[M+H-C_4H_8-CO_2]^+$, 219 (21), 203 (86), 135 (34), 119 (25), 91 (77) $[PhCH_2^+]$, 57 (100) $[C_4H_9^+]$; HRMS (CI^+, m/z): calculated for $C_{15}H_{14}O_5N_2SBr$ $[M+H-C_4H_8]^+$: 412.98069 amu. Found: 425.97974 ± 0.00128 amu.

***tert*-Butyl (7*R*,7a*R*)-1,6-dioxo-7-[(2-phenylacetyl)amino]-1,6,7,7a-tetrahydro-2*H*-1λ⁴-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (14e)**

Sulfoxide **14e** was prepared in the same manner as described for sulfoxide **14a**. Starting from sulfide **13e** (0.030 g; 0.08 mmol). Compound **14e** (0.017 g; 61%) was obtained as white amorphous solid after column chromatography (SiO_2, ethyl acetate / heptane 7:3). An analytical sample was obtained by recrystallization from ethyl acetate.

Mp >215°C (dec.); $[\alpha]_D$ = +146.6° (c = 0.21; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.53 (s, 9H, $C(CH_3)_3$), 3.19 (dt, *J* = 19.0 Hz ^4J ~ 2.0 Hz, 1H, SCH_2), 3.63 and 3.66 (qAB, J_{AB} = 16.2 Hz, 2H, $PhCH_2$), 3.78 (dd, *J* = 19.0 Hz *J* = 6.3 Hz, 1H, SCH_2), 4.45 (dd, *J* = 4.9 Hz ^4J ~ 1.6 Hz, 1H, NHCHC*H*S), 6.06 (dd, *J* = 4.9 Hz *J* = 9.8 Hz, 1H, NHC*H*CHS), 6.24 (dd, *J* = 6.3 Hz *J* = 2.4 Hz, 1H, =CH), 6.86 (d, *J* = 9.8 Hz, 1H, NH), 7.25-7.39 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 43.3 ($PhCH_2$)*, 43.9 (SCH_2)*, 59.9 (CHNH), 67.2 (CHS), 83.5 ($C(CH_3)_3$), 111.5 (=CH), 127.5, 128.9, 129.3 and 133.7 (PhC), 129.9 (=CCO_2^tBu), 159.2 (CO_2^tBu), 163.4 (C=O, lactam), 171.3 ($PhCH_2C(O)$) (*: signals may have interchanged); IR (KBr): ν 3219 (broad, NH), 1786 (C=O, lactam), 1721 (C=O, ester), 1658 and 1539 (C=O, amide), 1368 (C-N), 1156 (C-O, ester), 1024 (S=O) cm^{-1}; MS (CI^+): *m/z* (%) = 419 (1) $[M+C_2H_5]^+$, 405 (1) $[M+CH_3]^+$, 390 (1) $[M+H]^+$, 335 (13) $[M+H-C_4H_8]^+$, 287 (11), 176 (11), 136 (22), 118 (12), 91 (57) $[PhCH_2^+]$, 57 (100) $[C_4H_9^+]$; HRMS (CI^+, m/z): calculated for $C_{19}H_{22}O_5N_2S$ $[M+H]^+$: 391.13725 amu. Found: 391.13698 ± 0.00115 amu.

***tert*-Butyl (7*R*,7a*R*)-3-chloro-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (15a)**

To a pre-cooled (0°C) solution of sulfoxide **14a** (0.100 g; 0.235 mmol) in acetone sodium iodide (0.084 g; 0.56 mmol) and trifluoroacetic anhydride (0.1 g; ca. 2 equiv.) were successively added. After completion (1.5h), a saturated bicarbonate solution and ethyl acetate were added and the aqueous layer was extracted with ethyl acetate (2x10 ml). The combined organic layers were washed with brine, dried (MgSO4) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, ethyl acetate / hexane 2:1) giving **15a** (0.066 g; 69%) as a jelly compound. An analytical sample was obtained by stirring **15a** in di*iso*propyl ether and evaporation of the solvents *in vacuo*.

Mp 105-107°C (dec.); $[\alpha]_D$ = +272.6° (c = 0.135; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.53 (s, 9H, $C(CH_3)_3$), 3.52 and 3.74 (qAB, J_{AB} = 18.4 Hz, 2H, SCH_2), 3.61 (s, 2H, $PhCH_2$), 4.97 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 5.85 (dd, *J* = 4.9 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.85 (d, *J* = 9.2 Hz, 1H, NH), 7.26-7.33 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 30.8 (SCH_2), 43.0 ($PhCH_2$), 57.1 (CHNH), 58.7 (CHS), 84.1 ($C(CH_3)_3$), 123.4 (=CCl), 125.6 (=CCO_2^tBu), 127.4, 128.9, 129.2 and 134.0 (PhC), 159.0 (CO_2^tBu), 164.5 (C=O, lactam), 171.5 ($PhCH_2C(O)$); IR (KBr): ν 3275 (broad, NH), 1777 (C=O, lactam), 1725 (C=O, ester), 1657 and 1537 (C=O, amide), 1369 (C-N), 1154 (C-O, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 409 (3) $[M+H]^+$, 381 (6) $[M+H-CO]^+$, 353 (10) $[M+H-C_4H_8]^+$, 307 (5) $[M+H-C_4H_8-CO_2]^+$,

273 (4) [M+H-C_4H_8-CO_2-Cl]$^+$, 234 (26), 176 (99), 91 (100) [$PhCH_2^+$], 57 (96) [$C_4H_9^+$]; HRMS (CI$^+$, m/z): calculated for $C_{19}H_{21}O_4N_2SCl$ [M+H]$^+$: 409.09888 amu. Found: 409.09848 ± 0.00123 amu.

***tert*-Butyl (7*R*,7a*R*)-3-bromo-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (15b)**

Bromo derivative **15b** was prepared analogously to **15a** from its sulfoxide **14b** (0.068 g; 0.14 mmol), yielding, after purification, sulfide **15b** (0.067 g; 50%) as a jelly compound.

Mp 142-144°C; $[\alpha]_D$ = +62.6° (c = 0.61; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.50 (s, 9H, $C(CH_3)_3$), 3.61 and 3.64 (qAB, J_{AB} = 15.7 Hz, 2H, $PhCH_2$), 3.62 and 3.83 (qAB, J_{AB} = 18.4 Hz, 2H, SCH_2), 5.00 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 5.83 (dd, *J* = 4.9 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.53 (d, *J* = 9.2 Hz, 1H, NH), 7.25-7.37 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 27.8 ($C(CH_3)_3$), 32.4 (SCH_2), 43.1 ($PhCH_2$), 57.0 (CHNH), 59.2 (CHS), 84.3 ($C(CH_3)_3$), 110.6 (=CBr), 127.4 (=CCO_2^tBu), 127.6, 129.0, 129.3 and 133.8 (PhC), 159.6 (CO_2^tBu), 163.8 (C=O, lactam), 171.3 ($PhCH_2C(O)$); IR (KBr): ν 3331 (broad, NH), 1759 (C=O, lactam), 1725 (C=O, ester), 1681 and 1534 (C=O, amide), 1368 (C-N), 1154 (C-O, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 481 (1) and 483 (1) [M+C_2H_5]$^+$, 452 (1) and 454 (1) [M$^+$], 397 (2) and 399 (2) [M+H-C_4H_8]$^+$, 319 (2) [M+H-C_4H_8-Br]$^+$, 273 (13), 176 (60), 91 (46) [$PhCH_2^+$], 57 (100) [$C_4H_9^+$]; HRMS (CI$^+$, m/z): calculated for $C_{19}H_{21}O_4N_2SBr$ [M+H]$^+$: 453.04838 amu. Found: 453.04767 ± 0.00136 amu.

***tert*-Butyl (7*R*,7a*R*)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (15e)**

Hydrogen compound **15e** was prepared analogously to **15a** from its sulfoxide **14e** (0.200 g; 0.51 mmol), yielding, after purification, sulfide **15e** (0.138 g; 72%) as a white solid. An analytical sample (colorless plates) was obtained by crystallization from ethyl acetate / heptane.

Mp 151-153°C; $[\alpha]_D$ = +118.1° (c = 0.54; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.51 (s, 9H, $C(CH_3)_3$), 3.39 and 3.50 (qAB, J_{AB} = 19.1 Hz *J* = 6.2 Hz *J* = 2.6 Hz, 2H, SCH_2), 3.62 (qAB, J_{AB} = 15.9 Hz, 2H, $PhCH_2$), 4.88 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.89 (dd, *J* = 5.0 Hz *J* = 9.3 Hz, 1H, NHC*H*CHS), 6.37 (dd, *J* = 6.2 Hz *J* = 2.6 Hz, 1H, =CH), 6.94 (d, *J* = 9.3 Hz, 1H, NH), 7.23-7.34 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 24.0 (SCH_2), 27.8 ($C(CH_3)_3$), 43.0 ($PhCH_2$), 56.8 (CHNH), 59.3 (CHS), 82.8 ($C(CH_3)_3$), 118.5 (=CH), 129.1 (=CCO_2^tBu), 127.2, 128.7, 129.2 and 134.1 (PhC), 160.5 (CO_2^tBu), 164.8 (C=O, lactam), 171.4 ($PhCH_2C(O)$); IR (KBr): ν 3323 (broad, NH), 1767 (C=O, lactam), 1719 (C=O, ester), 1662 and 1520 (C=O, amide), 1394 (C-N), 1150 (C-O, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 403 (1) [M+C_2H_5]$^+$, 374 (3) [M$^+$], 347 (4) [M+C_2H_5-C_4H_8]$^+$, 319 (19) [M+H-C_4H_8]$^+$, 176 (100), 144 (57), 91 (83) [$PhCH_2^+$], 57 (85) [$C_4H_9^+$]; HRMS (CI$^+$, m/z): calculated for $C_{19}H_{22}O_4N_2S$ [M+H]$^+$: 375.13785 amu. Found: 375.13714 ± 0.00113 amu.

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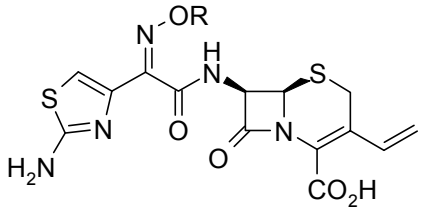
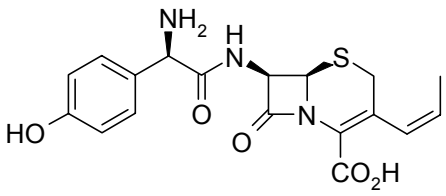
6 WITTIG-TYPE REACTIONS WITH 3-FORMYLCEPHALOSPORINS

6.1 Introduction

Due to the important role that cephalosporin antibiotics still play in current medical practice, considerable effort has been invested in the search for cephalosporin derivatives with improved therapeutic properties. β-Lactam antibiotics, which show an improved biological activity, are cephalosporins substituted with an alkene at the C_3-position.



1 R = H (cefdinir)
2 R = CH_2CO_2H (cefixime)



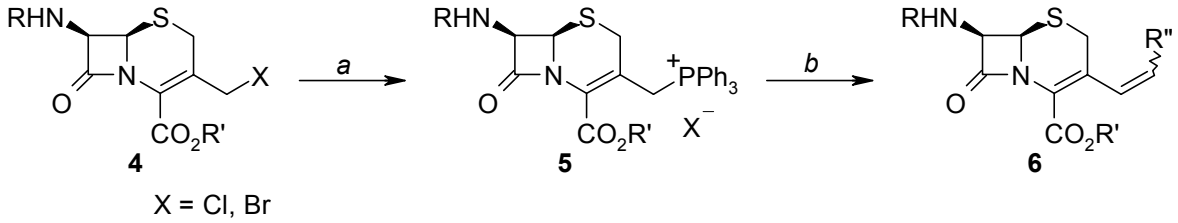
3 cefprozil

Figure 1.

Important members of this family of 3-alkenylcephalosporins, which are active against both Gram-positive and Gram-negative bacteria, are cefdinir (**1**), cefixime (**2**)

and cefprozil (**3**) (Figure 1). The discovery of these active, orally administrable cephalosporins has been a stimulus for increased synthetic activity aimed at finding new 3-alkenyl based cephalosporins.[1]

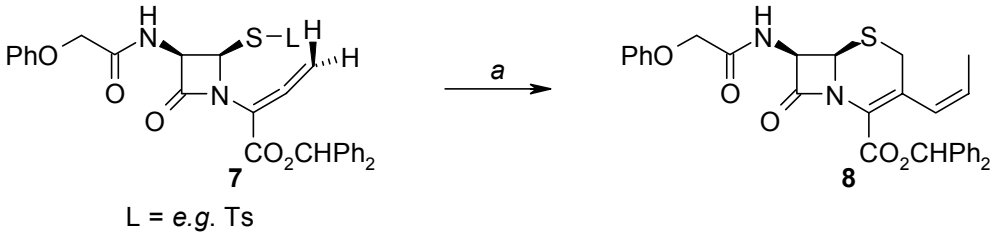
The most frequently employed synthesis to 3-alkenylcephalosporins **6** starts with a properly protected C_{10}-halogenated cephalosporin **4**, which is converted into the corresponding phosphonium derivative **5**. This salt **5** is then applied in a conventional Wittig reaction with an aldehyde, or in an epoxide mediated Wittig reaction (Scheme 1).[2],[3]



a) PPh_3, CH_2Cl_2; b) R"CHO, base or epoxide.

Scheme 1.

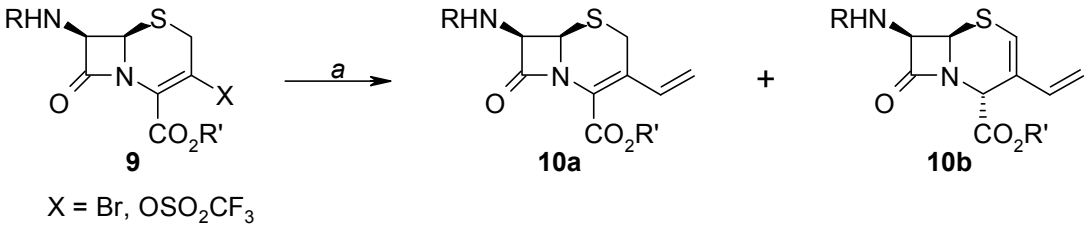
Hitherto, several syntheses of cefprozil (**3**) have been reported.[2],[4] Recently, Farina[5] and Torii[6] have developed new methodologies for the synthesis of 3-vinyl-cephems **8**. Starting from the readily available penicillin V sulfoxide diphenylmethyl ester, allenylazetidinones **7**[7] were synthesized, which were transformed in **8** by subsequent reaction with alkenyltributyltin compounds[7] or organocuprates[8] (Scheme 2).



a) [(Z)-propenyl]$_2$CuLi, THF, -78°C, 1h, 55%.

Scheme 2.

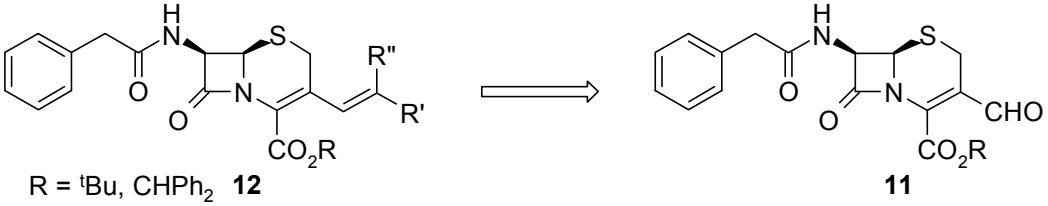
In addition, high-yielding palladium-catalyzed coupling reactions of organotin compounds with 3-triflioxy cephems[9] and cross-coupling reactions of 3-sulfonato or 3-bromo-cephems **9** with alkenyltin reagents to vinylcephems **10** have been described (Scheme 3).[10]



a) allylSnBu$_3$, Pd(OAc)$_2$, LiI, Et$_3$N, NMP, r.t., 85-93%.

Scheme 3.

Until now, only a few 3-alkenylcephalosporins **12** have been synthesized from the corresponding 3-formylcephalosporins **11**.[11],[12] In this approach the aldehyde compound of the Wittig reaction is present in the cephalosporin substrate, whereas in the abovementioned synthesis the ylide was part of the *β*-lactam unit. In almost all reported examples, aldehyde **11** is coupled with stabilized phosphorous ylides. In this chapter, a general approach to 3-alkenylcephalosporins **12** from readily available 3-formylcephalosporins **11** is described (Scheme 4). In principle, this route to the cephalosporin core structures of cefdinir (**1**) and cefprozil (**3**) looks very attractive, as in principle stabilized as well as non-stabilized phosphorous ylides can be used for the olefination reaction.



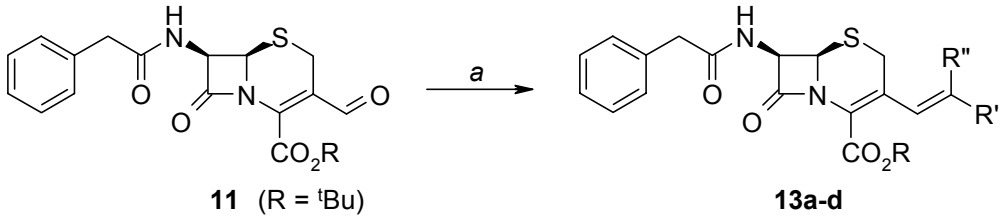
Scheme 4.

The main problem that may arise in the synthesis of 3-alkenyl *β*-lactams, employing the Wittig methodology, is the inevitable use of phosphorous ylides, which have both basic and nucleophilic properties. As a consequence, these Wittig reactions may lead to disintegration of the *β*-lactam core or result in mixtures of Δ^2/Δ^3-isomers.[13] An other important structural aspect is control of the geometry of the newly formed double bond. A high selective Wittig olefination is crucial, as *Z*- and *E*-isomers exert different antibacterial activity.

6.2 Results and discussion

6.2.1 Stabilized phosphorous ylides

Stabilized ylides can usually be handled at room temperature, unlike non-stabilized phosphorous ylides, and can be prepared without using strong bases (such as butyl lithium). These ylides do hardly have a basic character. The stability of these ylides has its origin in the strong electronic conjugation of the P=C bond with an ester, carbonyl or a nitrile π-system. In order to evaluate the Wittig olefination of aldehyde **11** (R = ^{t}Bu) in a general sense, the first experiments were carried out with stabilized phosphorous ylides,[12] in order to avoid possible base induced side reactions (Scheme 5). Aldehyde **11** was synthesized as described in chapter 3. The results of the Wittig reactions are shown in Table 1.



11 (R = ^{t}Bu) **13a-d**

a) Ph_3P=CR', CH_2Cl_2, 0°C, 4-8h.

Scheme 5.

Table 1: *Wittig olefination of 3-formylcephalosporin **11**.*

entry:	ylide:	R' =	R" =	product[c] (%):	
1	Ph_3P=CHCO_2Et	CO_2Et	H	**13a**	51[a]
2	Ph_3P=CHCN	CN	H	**13b**	53[a]
3	Ph_3P=CHC(O)Me	C(O)Me	H	**13c**	0[b]
4	Ph_3P=C(Me)CO_2Et	CO_2Et	Me	**13d**	0[b]

[a] yields not optimized

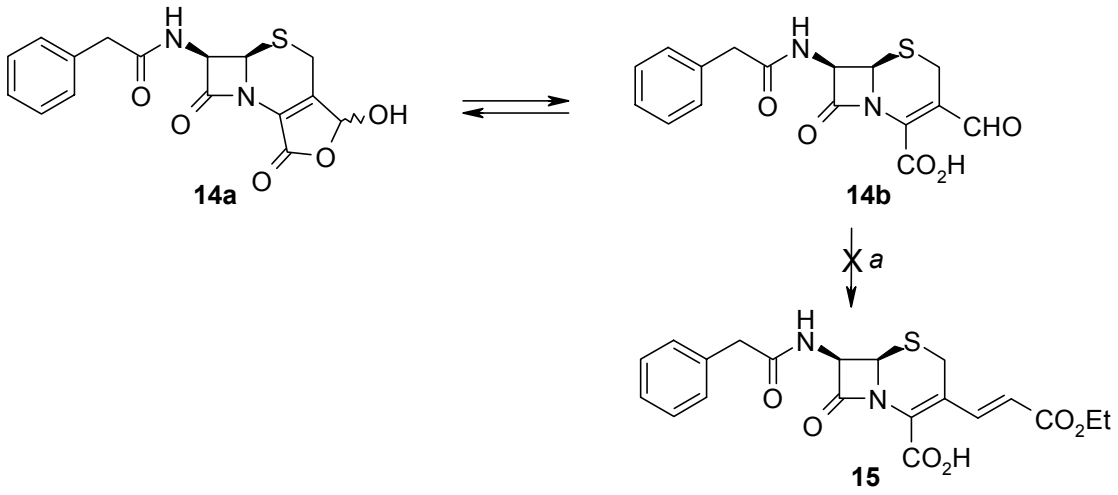
[b] no reaction; only starting material recovered

[c] >99% *trans* selectivity (no *cis* products observed)

The data in this Table 1 clearly reveal that the nature of the applied ylide subtly determines the outcome of the reaction. While ethyl 2-(triphenylphosphanylidene)acetate and 2-(triphenylphosphanylidene)acetonitrile (entries 1 and 2) leads to the desired Δ^3-isomers **13a** and **13b** in acceptable yield and high *E*-selectivity,[14] the ylides 1-(triphenylphosphanylidene)acetone and ethyl 2-(triphenylphosphanylidene)propanoate (entries 3 and 4) did not react at all at 0°C.

Increasing the temperature to room temperature led in the first three cases to considerable decomposition of the starting aldehyde **11** and to a diminished selectivity in the olefination of **11** in entries 1 and 2. Also the use of two equivalents of phosphorane did not help, but led to less selectivity (partly isomerization to Δ^2-product) or a lower yield. The presence of an extra methyl group in ethyl 2-(triphenylphosphanylidene)propanoate (entry 4) did not result in any reaction, probably due to a lower reactivity of this ylide caused by severe steric hindrance. Raising the temperature to 40°C, or even performing the reaction in toluene at reflux temperature, did not lead to any reaction with this ylide, and only a little amount of starting material **11** was recovered. These results show that stabilized ylides are not very reactive neither as nucleophile, nor as a base, because no isomerized (Δ^2-) products were isolated at 0°C.

Disappointingly, Wittig reactions of the hydroxycephalolactone **14a**, which is obtained after deprotection of the *tert*-butyl ester of aldehyde **11** and is supposed to be equivalent with the open aldehyde structure **14b**, with stabilized phosphoranes were also not successful (Scheme 6). Even attempts to perform the reaction in refluxing toluene, or by using 2.2 equivalents of ylide, did not lead to any noticeable conversion, and starting material **14a** was recovered.

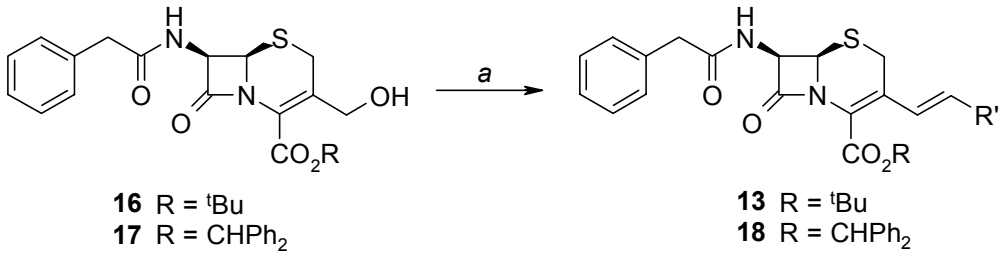


a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2 (r.t.) or toluene (reflux), 4-8h.

Scheme 6.

6.2.2 Direct conversion of 3-hydroxymethylcephalosporins into Wittig products

Recently, Taylor *et al.*[15] described an oxidative Wittig process in which (non)-activated alcohols were treated with manganese(IV) oxide in the presence of a stabilized Wittig reagent. The essential feature of this methodology is that the alcohol is oxidized *in situ* to the corresponding aldehyde, which then is immediately entrapped by the Wittig ylide. This process is particular usefully in those cases where the corresponding aldehyde is unstable, or difficult to isolate or purify. The 3-hydroxymethylcephalosporins **16** and **17** are readily available (see chapter 3), and therefore they are attractive substrates for this oxidative Wittig reaction for the synthesis of 3-alkenylcephalosporins **13** (Scheme 7). The results of this direct Wittig olefination of 3-hydroxymethyl compounds **16** and **17** are collected in Table 2.



a) MnO_2, CH_2Cl_2, 1.2 equiv. $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCN$, r.t., 8h.

Scheme 7.

Table 2: *Direct Wittig olefination of 3-hydroxymethylcephalosporins **16** and **17**.*

entry:	alcohol:	R =	ylide:	R' =	product (%)[a]:	
1	**16**	^{t}Bu	$Ph_3P{=}CHCO_2Et$	CO_2Et	**13a**	39
2	**16**	^{t}Bu	$Ph_3P{=}CHCN$	CN	**13b**	39
3	**17**	$CHPh_2$	$Ph_3P{=}CHCO_2Et$	CO_2Et	**18a**	30
4	**17**	$CHPh_2$	$Ph_3P{=}CHCN$	CN	**18b**	32

[a] overall yield; reactions not optimized

Although the overall yields of the oxidative olefination of the alcohols are moderate, this methodology could indeed successfully be applied to cephalosporin alcohols. The yields for the *tert*-butyl esters **13** are slightly better than those for the benzhydryl esters **18**, which is in line with other reported Wittig reactions with 3-formylcephems.[16] The somewhat lower yields must be due to a less effective olefination of the *in situ* formed aldehyde, as the oxidation of the 3-

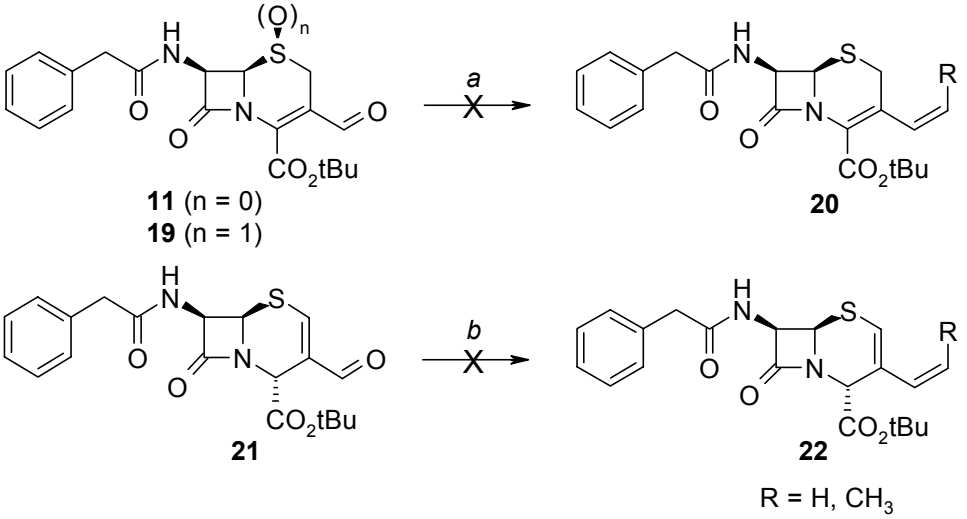
hydroxymethylcepahlosporins with manganese(IV) oxide to the corresponding formyl compound is usually a high yielding reaction.[17]

Attempts to use IBX or the Dess-Martin periodide instead of manganese(IV) oxide in this olefination process,[18] were not successful for the *β*-lactams. No trace of the desired olefins could be isolated after work-up, instead severe decomposition was observed. Apparently, these combinations of oxidants and Wittig reagents are not allowed for the sensitive cephalosporin system.

6.2.3 Non-stabilized phosphorous ylides

In order to have access to the core structures of cefdinir (**1**) and cefprozil (**3**), Wittig olefination of aldehyde **11** (R = ^{t}Bu) with non-stabilized phosphoranes is the obvious choice. These ylides, which require strong bases (*e.g.* BuLi) for their preparation, usually favor the formation of *Z*-alkenes (as is present in cefprozil **3**). Epoxides, which are commonly used in the dehydrohalogenation of phosphonium salts in Wittig reactions[3],[19] cannot be applied in the present case as they are not sufficiently reactive to produce the ylides from the corresponding phosphonium salts.

The results of the attempted Wittig reactions with non-stabilized ylides (Scheme 8) are summarized in Table 3. The ylides were prepared by addition of butyllithium to a solution of 1.5 equivalents of phosphonium salt in THF at -30°C (or at 0°C) under a nitrogen atmosphere. The appearance of a strongly yellow color indicated the formation of the ylides.



Scheme 8.

Table 3: *Wittig olefination of 3-formylcephalosporins **11**, **19**, and **21** using non-stabilized ylides*

entry:	aldehyde:	ylide:	R =	conditions:	result:
1	**11**	$Ph_3P=CH_2$	H	-78°C → 0°C	severe decomposition
2	**11**	$Ph_3P=CH_2$	H	-78°C, quenching with HCl (aq)	decomposition
3	**19**	$Ph_3P=CHCH_3$	Me	-78°C[a]	decomposition
4	**21**	$Ph_3P=CHCH_3$	Me	-78°C	decomposition and **21** (recovery)

[a] also addition of the ylide to the aldehyde led to decomposition

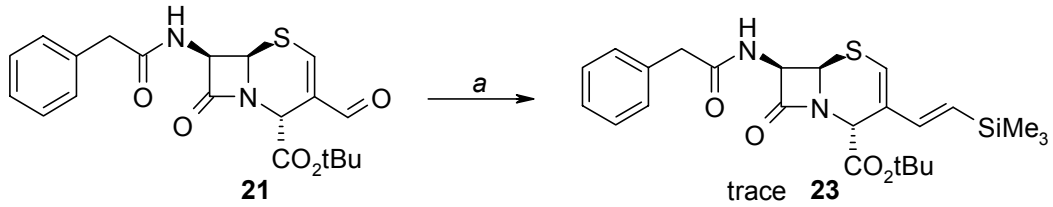
None of these olefinations was successful, either complete decomposition of the starting material was observed or recovery of starting aldehyde up to 40% in the case of substrate **21**. Even at -78°C, aldehydes **11** and **19** had completely decomposed within 10 minutes. Immediately after the addition of ylide, the reaction mixture turned strongly dark brown to black. The corresponding Δ^2-isomer **21** is slightly less unstable, because complete decomposition was only observed after 1 hour (at -78°C). The non-stabilized phosphorous ylides used here are relatively strong bases and reactive nucleophiles, which probably causes the unwanted opening of the *β*-lactam ring, which is then followed by a cascade of decomposition reactions.

The unfortunate conclusion of the above described experiments is that the desired syntheses of the cores of cefdinir (**1**), cefixime (**2**), and cefprozil (**3**) *via* a Wittig

olefination of 3-formylcephalosporins using non-stabilized phosphoranes cannot be accomplished.

6.2.4 Alternative approaches to the synthesis of the core structures of cefixime and cefdinir

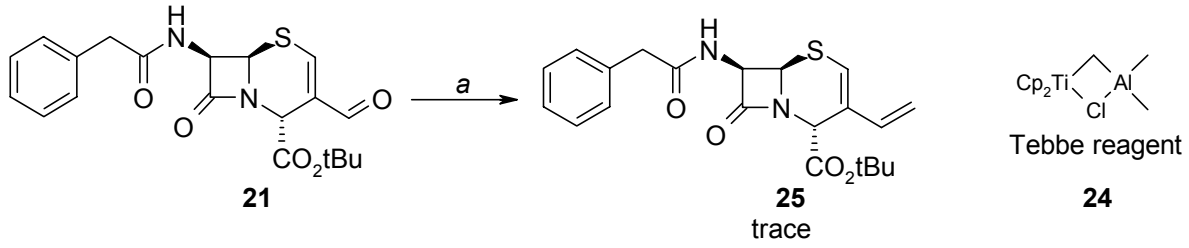
As is described above, the Wittig approach to the 3-alkenylcephalosporins from 3-formylcephalosporins is not successful. Therefore, other methods to accomplish the desired transformation were considered. First, the recently reported one-pot conversion of aldehydes into *E*-alkenylsilanes using iodoform, manganese, trimethylsilyl chloride and a catalytic amount of chromium(II) chloride[20] was tried with the 3-formylcephalosporins (Scheme 9). Disappointingly, the Δ^3-isomer **11** led only to decomposition, whereas the Δ^2-analogue **21** gave only a trace of the silyl alkene **23**, which was identified by ^{1}H-NMR analysis. This approach was abandoned because of the very low yield.



a) CHI_3, Mn, Me_3SiCl, $CrCl_2$ (cat.), THF, r.t., 24h.
Scheme 9.

Secondly, the so-called Tebbe reaction was examined for the introduction of a methylene group. The Tebbe reagent $Cp_2TiCH_2{\cdot}AlMe_2Cl$ (**24**),[21] is a source of the reactive titanium methylene species "$Cp_2Ti{=}CH_2$", which is actually the species responsible for the methylation.[22] The formation of this methylene intermediate is accelerated by THF or pyridine. The driving force of this process is the high oxophilicity of titanium. The scope of the reaction is larger than for the corresponding phosporanes.[23] Even esters and imides are converted into vinyl ethers and enamines by the Tebbe reagent.[24] The major advantage of this approach, as compared with the use of phosphoranes, is the lower basicity of the titanium reagent. Therefore, the Tebbe reaction may be applicable in the case of cephalosporin aldehydes, although nucleophilic opening of the β-lactam ring still may be a serious problem. Indeed, aldehydes **11** and **19**, with the double bond in the Δ^3-position, led

to a very fast uncontrolled reaction as was indicated by the instantaneous blackening of the reaction mixture after addition of the Tebbe reagent **24** at -78°C.



a) Tebbe reagent **24**, *THF, -78°C, 1%.*
Scheme 10.

Only 3-formylceph-2-em **21** gave, besides various decomposition products, the desired methylene compound **25**, albeit in a very low yield of 1% (Scheme 10). Both mass and ^{1}H-NMR spectra were in agreement with this structure. Apparently, cephalosporin compounds are too sensitive for the Tebbe reaction. In spite of the relatively low basicity, the high nucleophilicity of the Tebbe reagent probably causes opening of the *β*-lactam ring, which is detrimental for a successful methylenation reaction.

6.3 Concluding remarks

The olefination reaction of 3-formylcephalosporins was successfully carried out with phosphorous ylides stabilized by conjugation, *viz*. for ester and cyano substituted ylides, in moderate yields of *ca*. 50%. In *β*-lactam chemistry, expeditious yield optimization studies frequently lead to improvements in yield. The direct olefination of 3-hydroxymethylcephalosporins employing the oxidative Wittig process could be accomplished with the same type of ylides in yields ranging from 32-39%. Disappointingly, the olefination of 3-formylcephalosporins with non-stabilized ylides was not met with success, only decomposition of the cephalosporin nucleus was observed. Alternative routes to 3-alkenylcephalosporins also failed to form the desired products.

6.4 Experimental part

General remarks

100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer and 300 MHz ^{1}H-NMR spectra and all ^{13}C-NMR spectra were recorded on a Bruker AC 300 using Me_4Si as internal standard. All coupling constants are given as ^{3}J in Hz, unless indicated otherwise. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FTS-25 instrument. For mass spectra a double focusing VG7070E mass spectrometer was used. For some samples, High Resolution FAB was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer (JEOL Ltd. 1-2 Musashino 3-chome, Akishima Tokyo), coupled to a MS-MP 9021D/UPD data system (University of Amsterdam). Elemental analyses were conducted on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. For the determination of optical rotations a Perkin-Elmer 241 polarimeter was used. Solvents were dried using the following methods: dichloromethane was distilled from P_2O_5; ethyl acetate was distilled from K_2CO_3; hexane and heptane were distilled from CaH_2; tetrahydrofuran was distilled from sodium just before use. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on a Merck precoated silica gel 60 F254 plates (0.25 mm). Spots were visualized with UV or using a molybdate spray. Flash chromatography was carried out at a pressure of *ca*. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was performed with ACROS silicagel (0.035-0.070 mm; pore diameter ca. 6 nm).

Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada). Alcohol **17** was a generous gift of DSM Anti-Infectives, Delft. Aldehydes **11**, **19**, and **21** were prepared according to a known procedure.[17]

***tert*-Butyl (7*R*,7a*R*)-3-[(*E*)-3-ethoxy-3-oxo-1-propenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13a)**

Freshly prepared ethyl 2-(triphenylphosphanylidene)acetate (0.091 g; 0.26 mmol) was added in one portion to a cooled (0°C) and stirred solution of aldehyde **11** (0.10 g; 0.248 mmol) in dichloromethane (5 ml). After stirring at 0°C for another 4h, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, *n*-heptane/ethyl acetate 1:2), affording **13a** (0.060 g; 51%) as a white-yellow foam and a trace of aldehyde **11**.

Direct oxidation Wittig approach

Activated manganese(II) oxide (1.3 g; *ca*. 30 equivalents) was added in three portions at ambient temperature to a mixture of alcohol **16** (0.200 g; 0.494 mmol) and ethyl 2-(triphenylphosphanylidene)acetate (0.207 g; 0.593 mmol) in dichloromethane (7 ml). After complete conversion (4-8h), the reaction mixture was filtered over hyflo and concentrated *in vacuo*. Purification by column chromatography (SiO_2, *n*-heptane/ethyl acetate 1:2) afforded Wittig product **13a** (0.090 g; 39%) as a yellow foam.

Mp 94-96°C; $[\alpha]_D$ = -76.9° (c = 0.52; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.30 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.56 (s, 9H, $C(CH_3)_3$), 3.46 and 3.55 (qAB, J_{AB} = 17.7 Hz, 2H, SCH_2), 3.62 (s, 2H, $PhCH_2$), 4.22 (dq, *J* = 7.1 Hz ^{4}J = 2.3 Hz, 2H, CH_2CH_3), 4.95 (d, *J* = 5.0 Hz, 1H, NHCHCHS), 5.89 (dd, *J* = 5.0 Hz *J* = 9.3 Hz, 1H, NHCHCHS), 5.98 (d, *J* = 16.0 Hz, 1H, =$CHCO_2$Et), 6.67 (d, *J* = 9.3 Hz, 1H, NH), 7.26-7.37 (m, 5H, PhH), 7.87 (d, J = 16.0 Hz, 1H, CH=$CHCO_2$Et); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 14.2

(CH_2CH_3), 24.1 (SCH_2), 27.7 ($C(CH_3)_3$), 43.0 ($PhCH_2$), 57.6 (CHNH), 59.3 (CHS)*, 60.7 (CH_2CH_3)*, 84.4 ($C(CH_3)_3$), 120.3 (*C*H=CHCO$_2$Et), 120.8 (=*C*CH=CHCO$_2$Et), 127.5, 129.0, 129.3 and 133.8 (PhC), 130.3 (=*C*CO$_2$^{t}Bu), 139.0 (CH=*C*HCO$_2$Et), 160.0 (*C*O$_2$^{t}Bu), 164.6 (C=O, lactam), 166.0 (*C*O$_2$Et), 171.3 ($PhCH_2C(O)$) (*: signals may have interchanged); IR (KBr): ν 3339 (broad, NH), 1788 (C=O, lactam), 1711 and 1709 (C=O, esters), 1685 and 1534 (C=O, amide), 1367 (C-N), 1153 (C-O, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 495 (4) $[M+Na]^+$, 473 (3) $[M+H]^+$, 417 (12) $[M+H-C_4H_8]^+$, 298 (12), 242 (95), 176 (100), 91 (58) $[PhCH_2]^+$.

***tert*-Butyl (7*R*,7a*R*)-3-[(*E*)-2-cyano-1-ethenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13b)**

This compound was prepared in the same way as described for **13a**, starting from aldehyde **11** (0.17 g; 0.422 mmol) and triphenylphosphoranylidene acetonitrile (0.14 g; 0.46 mmol), yielding **13b** (0.096 g; 53%) as white needles after column chromatography (SiO_2, *n*-heptane/ethyl acetate 1:1), followed by crystallization from ethyl acetate / heptane.

Direct oxidation Wittig approach

Prepared in the same way as described for **13a**, starting from alcohol **16** (0.270 g; 0.667 mmol) and ylide (0.201 g; 0.80 mmol), giving **13b** as white needles (0.110 g; 39%).

Mp 147-149°C; $[\alpha]_D$ = -181.9° (c = 0.52; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.52 (s, 9H, $C(CH_3)_3$), 3.63 and 3.67 (qAB, J_{AB} = 16.0 Hz, 2H, $PhCH_2$), 3.79 and 4.13 (qAB, J_{AB} = 17.9 Hz, 2H, SCH_2), 4.99 (d, *J* = 5.3 Hz, 1H, NHCHC*H*S), 5.36 (d, *J* = 12.4 Hz, 1H, =CHCN), 5.93 (dd, *J* = 5.3 Hz *J* = 9.3 Hz, 1H, NHC*H*CHS), 6.28 (d, *J* = 9.3 Hz, 1H, NH), 7.26-7.40 (m, 6H, C*H*=CHCN and PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 25.1 (SCH_2), 27.7 ($C(CH_3)_3$), 43.3 ($PhCH_2$), 57.7 (CHNH), 59.7 (CHS), 84.9 ($C(CH_3)_3$), 96.8 (*C*HCN), 117.2 (CN), 123.4 (=*C*CH=CHCN), 127.8, 129.2, 129.4 and 133.5 (PhC), 131.3 (=*C*CO$_2$^{t}Bu), 143.5 (*C*H=CHCN), 159.9 (*C*O$_2$^{t}Bu), 164.5 (C=O, lactam), 171.1 ($PhCH_2C(O)$); IR (KBr): ν 3325 (broad, NH), 2267 (C≡N), 1789 (C=O, lactam), 1703 (C=O, ester), 1688 and 1534 (C=O, amide), 1367 (C-N), 1151 (C-O, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 426 (2) $[M+H]^+$, 370 (26) $[M+H-C_4H_8]^+$, 195 (33), 176 (48), 91 (46) $[PhCH_2^+]$, 57 (100) $[C_4H_9^+]$; HRMS (CI$^+$, m/z): calculated for $C_{22}H_{23}O_4N_3S$: 425.14090 amu. Found: 425.14011 ± 0.00128 amu.

Benzhydryl (7*R*,7a*R*)-3-[(*E*)-3-ethoxy-3-oxo-1-propenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (18a)

To a suspension of alcohol **17** (0.278 g; 0.54 mmol) and ethyl 2-(triphenylphosphanylidene)acetate (0.226 g; 0.648 mmol) in dichloromethane (10 ml) was added activated manganese(IV) oxide (1.4 g; *ca.* 30 equivalents) at room temperature. After completion (4-8h), the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, *n*-heptane/ethyl acetate 2:3) giving Wittig product **18a** (0.096 g; 30%) as a yellow-brown foam.

Mp 159-163°C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 3.59 and 3.66 (qAB, J_{AB} = 16.0 Hz, 2H, $PhCH_2$), 3.75 and 4.09 (qAB, J_{AB} = 18.0 Hz, 2H, SCH_2), 5.08 (d, *J* = 5.2 Hz, 1H, NHCHC*H*S), 5.90 (d, *J* = 16.0 Hz, 1H, =C*H*CO$_2$Et), 5.98 (dd, *J* = 5.2 Hz *J* = 9.1 Hz, 1H, NHC*H*CHS), 6.23 (d, *J* = 9.1 Hz, 1H, NH), 6.95 (s, 1H, $CHPh_2$), 7.24-7.40 (m, 15H, PhH), 7.87 (d, J = 16.0 Hz, 1H, C*H*=CHCO$_2$Et); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 14.1(CH_2CH_3), 25.1(SCH_2), 43.3($PhCH_2$), 57.7 (CHNH), 59.8 (CHS)*, 60.5 C*H*$_2$CH$_3$)* 80.1 *C*HPh$_2$), 120.4 *C*H=CHCO$_2$Et), 120.5 =*C*CH=CHCO$_2$Et), 127.0, 127.8, 128.1, 128.3, 128.5, 128.6, 128.8, 129.3, 129.4, 133.5, 138.5 and 138.8 (PhC), 129.4 (=*C*CO$_2$CHPh$_2$), 139.0 (CH=CHCO$_2$Et), 159.9 (*C*O$_2$CHPh$_2$), 164.5 (C=O, lactam), 171.3 ($PhCH_2C(O)$) (*: signals may have interchanged); IR

(KBr): ν 3276 (broad, NH), 1785 (C=O, lactam), 1713 and 1705 (C=O, esters), 1665 and 1524 (C=O, amide), 1351 (C-N), 1228 (C-O, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 583 (0.3) $[M+H]^+$, 492 (2) $[M+H-CHPh_2]^+$, 217 (50), 167 (100) $[CHPh_2^+]$, 91 (52) $[PhCH_2^+]$.

Benzhydryl (7*R*,7a*R*)-3-[(*E*)-2-cyano-1-ethenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (18b)

This compound was prepared in the same manner as described for compound **18a**, starting from alcohol **17** (0.515 g; 1.0 mmol), and triphenylphosphoranylidene acetonitrile (0.331 g; 1.10 mmol). After work-up and purification pure **18b** (0.172 g; 32%) was obtained.

Mp 180-182°C (dec.); $[\alpha]_D$ = -175.6° (c = 0.23; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 3.60 and 3.65 (qAB, J_{AB} = 16.0 Hz, 2H, $PhCH_2$), 3.77 and 4.10 (qAB, J_{AB} = 18.1 Hz, 2H, SCH_2), 5.0 (d, *J* = 5.1 Hz, 1H, NHCHC*H*S), 5.23 (d, *J* = 12.4 Hz, 1H, =CHCN), 5.94 (dd, *J* = 5.1 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.25 (d, *J* = 9.2 Hz, 1H, NH), 6.95 (s, 1H, $CHPh_2$), 7.11 (d, *J* = 12.4 Hz, 1H, C*H*=CHCN), 7.24-7.40 (m, 15H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 25.2 (SCH_2), 43.2 ($PhCH_2$), 57.7 (CHNH), 59.8 (CHS), 80.2 ($CHPh_2$), 97.5 (CHCN), 116.9 (CN), 122.2 (=CCH=CHCN), 126.9, 127.7, 128.0, 128.3, 128.4, 128.5, 128.6, 129.2, 129.4, 133.5, 138.4 and 138.7 (PhC), 129.6 ($=CCO_2CHPh_2$), 143.3 (CH=CHCN), 160.4 (CO_2CHPh_2), 164.8 (C=O, lactam), 171.1 ($PhCH_2C(O)$); IR (KBr): ν 3276 (broad, NH), 2267 (C≡N), 1784 (C=O, lactam), 1725 (C=O, ester), 1660 and 1521 (C=O, amide), 1350 (C-N), 1224 (C-O, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 536 (0.1) $[M+H]^+$, 369 (1) $[M+H-CHPh_2]^+$, 279 (32), 217 (50), 167 (100) $[CHPh_2^+]$, 136 (71), 91 (43) $[PhCH_2^+]$.

***tert*-Butyl (4*R*,7*R*,7a*R*)-6-oxo-7-[(2-phenylacetyl)amino]-3-vinyl-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (25)**

Tebbe's reagent (**24**) in toluene (2.5 ml) was added to a cooled (-78°C) solution of aldehyde **21** (0.512 g; 1.27 mmol) in dry THF (10 ml). After stirring for 45 min. at -78°C, TLC analysis showed complete conversion of the starting material. Water (5 ml) and dichloromethane were added and after separation of the organic layer, drying ($MgSO_4$) and concentration *in vacuo*, the residue was purified by column chromatography (SiO_2, ethyl acetate/heptane 1:1), giving methylene compound **25** (4.0 mg; 1%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.47 (s, 9H, $C(CH_3)_3$), 3.66 and 3.68 (qAB, J_{AB} = 16.0 Hz, 2H, $PhCH_2$), 5.04 (d, *J* = 11.3 Hz, 1H, CH=CH_cH_t), 5.08 (s, 1H, SCH=), 5.28 (d, *J* = 14.3 Hz, 1H, CH=CH_cH_t), 5.37 (d, *J* = 4.0 Hz, 1H, NHCHC*H*S), 5.66 (dd, *J* = 4.0 Hz *J* = 8.8 Hz, 1H, NHC*H*CHS), 6.15 (d, *J* = 8.8 Hz, 1H, NH), 6.22 (dd, *J* = 14.3 Hz *J* = 11.3 Hz, 1H, C*H*=CH_2), 6.23 (s, 1H, =C*H*$CO_2{}^t$Bu), 7.26-7.37 (m, 5H, PhH).

6.5 References and notes

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7 DIASTEREOSELECTIVE BARBIER TYPE ORGANOZINC ADDITIONS TO 3-FORMYLCEPHALOSPORINS

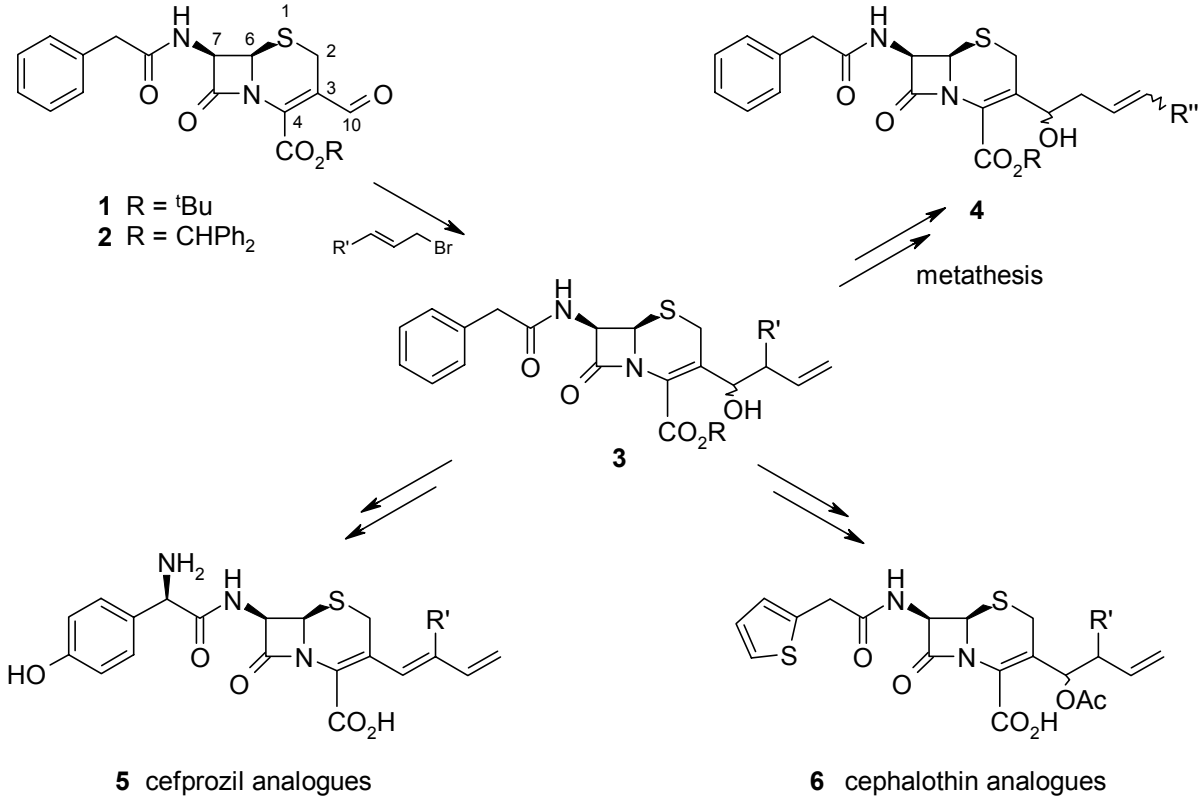
7.1 Introduction

The addition of carbon nucleophiles to carbonyl groups is one of the most frequently used methods for constructing carbon-carbon bonds.[1] A typical example is the allylation of aldehydes and ketones applying appropriate organometallic compounds.[2] The Grignard and Barbier-type organometallic additions are illustrative in these transformations. Allylic halides, which are difficult to transform into the corresponding Grignard reagents, frequently give excellent results applying the Barbier procedure[3] in which the organometallic intermediate is generated *in situ* in the presence of the carbonyl group.[4] The possibility of conducting these Barbier-Grignard type reactions in aqueous media has a great advance as no anhydrous organic solvents are needed. Moreover, the synthetic procedure does not require special safety precautions.[5],[6]

So far, organometallic additions to 3-formylcephalosporins have been reported only for Grignard-type reactions affording the corresponding carbinols as mixtures of diastereomers without significant diastereoselectivity. The only examples reported are additions with methyl-, ethyl-, and phenyl-magnesium bromide,[7] and with

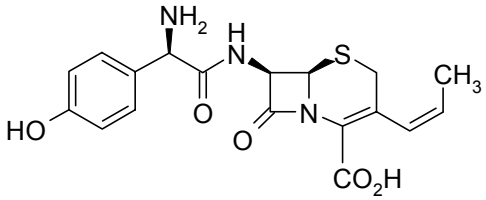
vinyl-, ethynyl-, and propynyl-magnesium bromide.[8],[9] For a more detailed overview of Grignard reactions with 3-formylcephaloporins, see Chapter 2. So far, scarce attention was paid to Barbier-type additions to 3-formylcephalosporins.[10]

As outlined in Scheme 1, the allylation of 3-formylcephalosporins offers attractive prospects for the synthesis of a variety of new 3-substituted cephalosporins. These types of alkenyl-substituted *β*-lactams are known to have potent anti-bacterial activity.

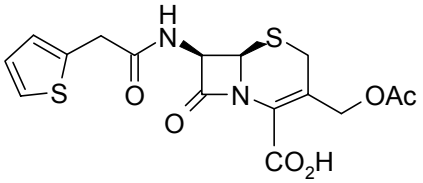


Scheme 1.

Starting from the readily available aldehydes **1** and **2**, the initially formed addition products **3** can be used as precursor for more complex cephalosporins. Metathesis with Grubb's catalyst offers new opportunities for further functionalization to **4**. In addition, the intermediate addition products **3** may be converted into cefprozil analogues **5** or cephalothin analogues **6** in a limited number of steps (Scheme 1). The parent antibiotics cefprozil (**7**) and cephalothin (**8**) are orally active antibiotics with desired properties (Figure 1).[11]



7 cefprozil



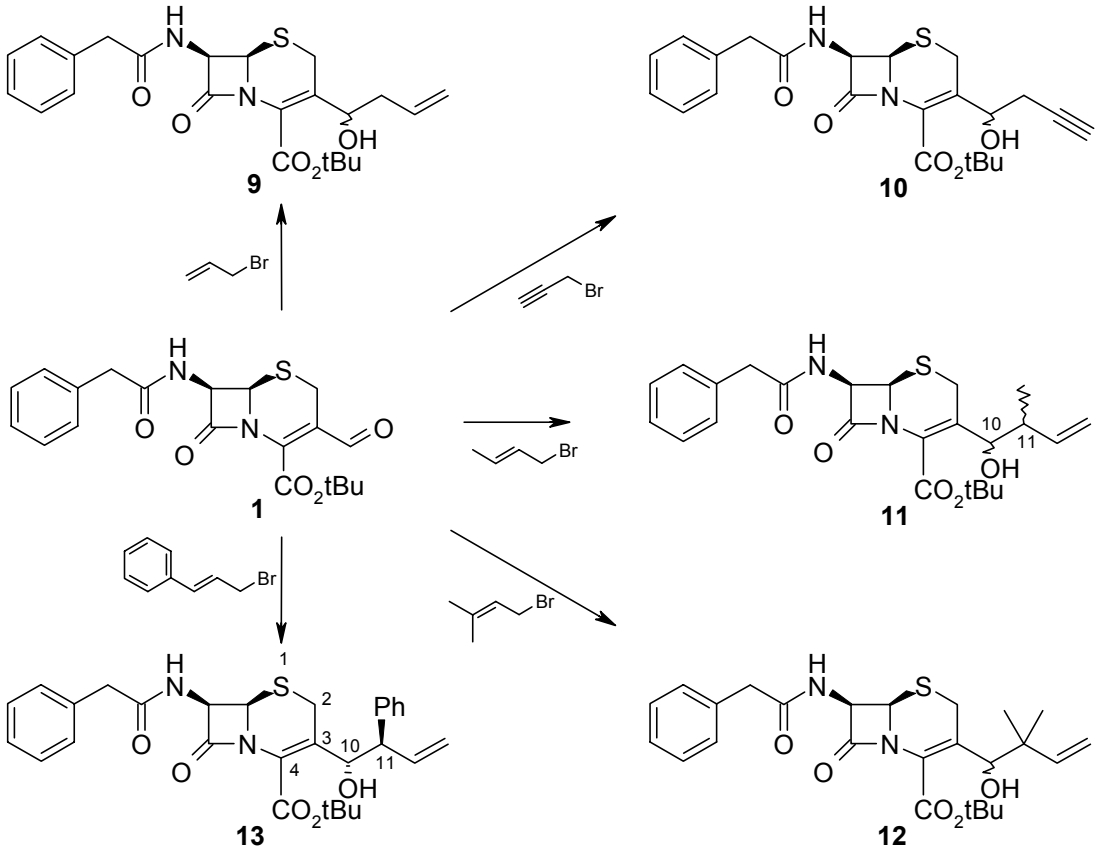
8 cephalothin

Figure 1.

In this chapter, the results of organozinc additions to 3-formylcephalosporins using the Barbier methodology are described. A preliminary study on possible applications of the obtained allylic carbinols is included as well.

7.2 Results and discussion

The zinc Barbier procedure was first applied to the allylation of 3-formylcephalosporin **1**. The reaction of **1**[12] with allyl bromide, non-activated zinc and saturated ammonium chloride in THF, resulted in homoallylic alcohol **9** in an excellent yield of 89% at room temperature (Scheme 2). At this temperature, two diastereomers were formed in a 25:75 ratio (fast-moving : slow-moving diastereomers on TLC). At 0°C, however, the reaction appeared to be highly diastereoselective. The ratio of homoallylic alcohols **9** now amounted to 10:90. In order to establish the scope of the reaction, other allylic bromides and also propargyl bromide were applied under similar conditions. In all cases the corresponding carbinols were produced in satisfactory yields, and with high diastereoselectivity (Table 1). Thus, the reaction of **1** with propargyl bromide afforded the homopropargyl alcohols **10** in 41% yield (diasteromeric ratio: 17:83 at ambient temperature). Again, the selectivity was improved to 10:90 when the reaction was performed at 0°C.



General reaction conditions: 2 equiv. bromide, 5 equiv. Zn dust, aqueous NH_4Cl, THF, 0°C or r.t.
Scheme 2.

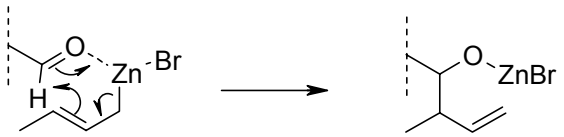
Table 1: *Barbier-type reactions of 3-formylcephalosporin **1**.*

entry:	bromide:	product:	yield (%):	ratio (0°C):	ratio (20°C):
1	allyl	**9**	89	10:90	25:75
2	propargyl	**10**	85	10:90	17:83
3	crotyl	**11**	79	50:50[b,c]	-[a]
4	prenyl	**12**	80	33:67	-[a]
5	cinnamyl	**13**	71	0:100[b,d]	10:90[b]

[a] reaction not performed
[b] ratio at C_{10}
[c] inseparable mixture (*syn* / *anti*) at C_{11}
[d] single isomer

The reaction of 3-formylcephalosporin **1** with crotyl bromide under Barbier conditions gave the methyl substituted homoallyl alcohol **11** in 79% yield in a 1:1 diastereomeric ratio. Clearly, the organozinc reagent derived from crotyl bromide has reacted in a different manner as initially expected. This product formation can be explained by an initial complexation of the organozinc reagent at the carbonyl

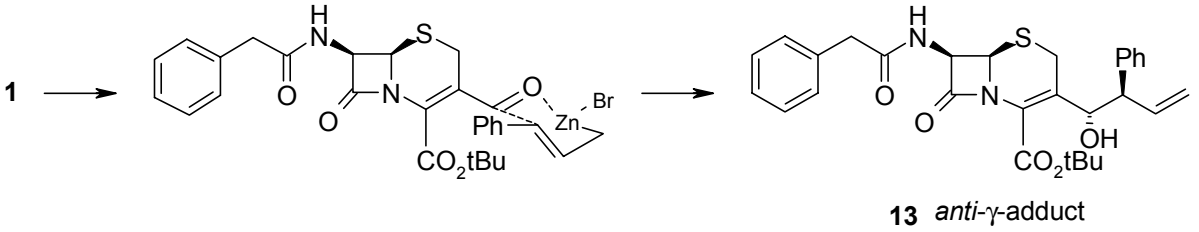
group, followed by a reaction at the carbonyl atom *via* a cyclic transition state as shown in Scheme 3.



Scheme 3.

It is conceivable that the reaction with allylzinc bromide follows a similar pathway. However, the diastereomeric ratio would then be in the range of 1:1. Therefore, the direct conventional reaction of the organometallic reagent surely will play a role as well. The organozinc reagent derived from propargyl bromide clearly reacts directly with aldehyde **1**, otherwise an allenic product would have been expected. The behavior of allylic organometallic reagents involving an attack resulting in a rearranged product have been encountered in the literature before.[13]

Similarly, the reaction of **1** with prenyl- and cinnamyl bromide resulted in the corresponding rearrangement products with a good to excellent diastereoselectivity (Table 1). Usually, reactions at ambient temperature showed a lower yield and a lower diastereoselectivity, therefore the reactions are preferably performed at 0°C. The reaction with cinnamyl bromide proceeds in a complete stereoselective manner. This preferred product formation can readily be explained by assuming that cinnamylzinc bromide reacts with aldehyde **1** *via* a six-membered cyclic transition state as depicted in Scheme 4. Usually, substituted allyl bromides in organozinc reactions result in an *anti*-diastereoselectivity (with respect to the extra chiral center), which is independent of the stereochemistry of the double bond in the allyl bromide moiety (Schemes 2 and 5). The alcohol function in cinnamyl adduct **13** was thus expected to be in an *anti*-relationship with respect to the phenyl group, as was confirmed by in-depth ^{1}H- and ^{13}C-spectroscopy (Scheme 4).

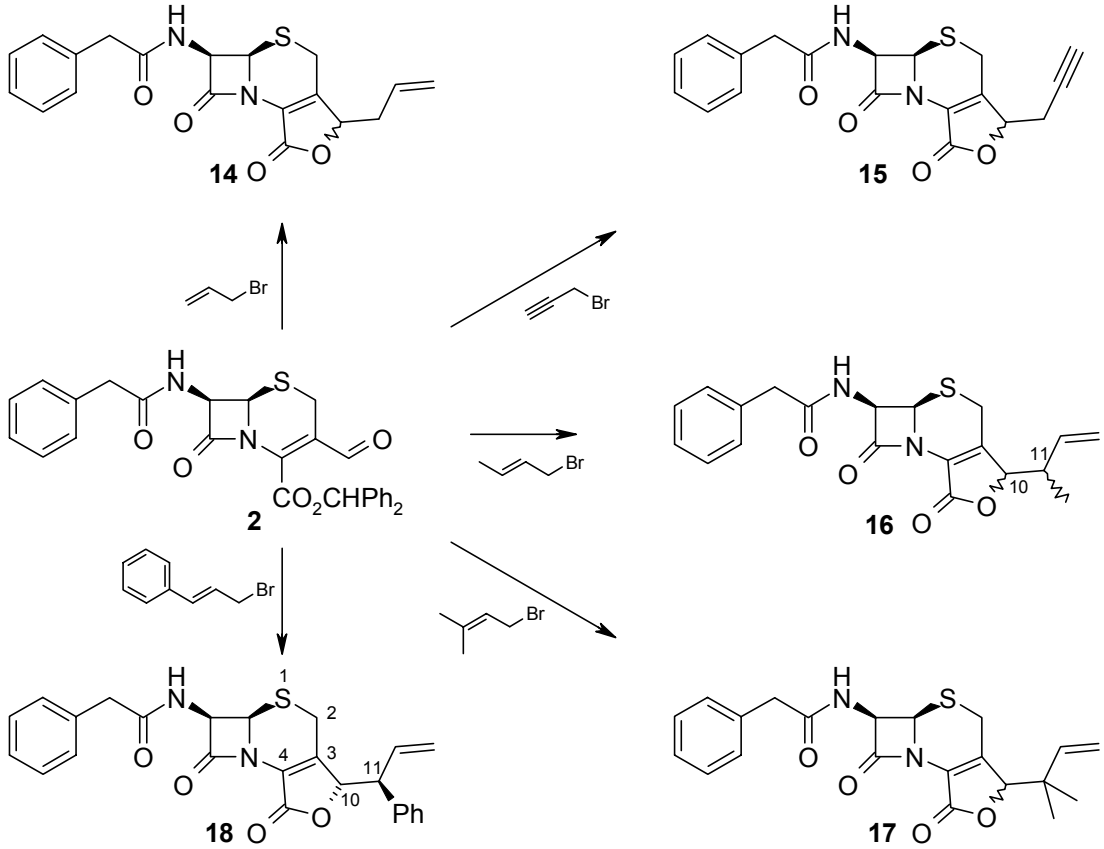


13 *anti*-γ-adduct

Scheme 4.

With the aim to study the steric influence of a different ester group at C_4, aldehyde **2**, containing at C_4 a diphenylmethyl ester, was synthesized.[14] Surprisingly, the reaction of aldehyde **2** with allyl bromide did not afford the expected homoallyl alcohols, but instead gave the corresponding lactones **14** in a good yield of 76% after purification. Even though TLC analysis showed the formation of the expected alcohols, the only products obtained after column chromatography were the lactones **14** as a mixture of diastereomers (Scheme 5; Table 2).

The formation of the lactones **14** is the result of an intramolecular transesterification of the initially formed homoallyl alcohols. Apparently, such transesterification does not take place with the *tert*-butyl ester products **10-13**. This difference in chemical behavior of two related esters again points to the sensitivity of cephalosporin substrates to subtle structural differences. The lactonization of the initially formed diphenylmethyl esters could not be avoided, even not under neutral conditions. A related facile lactonization was reported for a cephalosporin diphenylmethyl ester containing an acetoxy methyl group at C_3.[9] Lactone formation clearly is an easy process.



General reaction conditions: 2 equiv. bromide, 5 equiv. Zn dust, aqueous NH_4Cl, THF, 0°C or r.t.
Scheme 5.

Table 2: *Barbier-type reactions of 3-formylcephalosporin* **2**.

entry:	bromide:	product:	yield (%):	ratio (0°C):	ratio (20°C):
1	allyl	**14**	76	80:20	50:50
2	propargyl	**15**	95	98:02	67:33
3	crotyl	**16**	73	57:43[a]	-[c]
4	prenyl	**17**	87	70:30	-[c]
5	cinnamyl	**18**	70	100:0[b,d]	85:15

[a] inseparable mixture of 2 diastereomers (1:1) at C_{11}

[b] only trace amount of other isomer (TLC)

[c] not performed

[d] single isomer at C_{11}

The data in Table 2 reveal that in most cases the addition of the Barbier reagents to **2** is a highly diastereoselective process. These results are fully in line with those obtained for aldehyde **1** (*tert*-butyl ester) and those reported for 3-bromo-4-formylpyridine.[15] The relative configuration at C_{10} in the lactones was established by X-ray crystal structure analyses of the minor diastereomers of lactones **14** and **17** (Figure 4). From these X-ray studies, and by comparison of the ^{1}H-NMR structural characteristics, the configuration at C_{10} in other lactones **15**, **16**, and **18** could be established.

In the discussion of the stereochemical course of the reaction first the *relative* stereochemistry of the newly formed stereochemical centers at C_{10} and C_{11} in the reaction with cinnamylzinc bromide will be addressed. Assuming that the actual carbon-carbon bond formation proceeds *via* a cyclic transition state as depicted in Scheme 4, the preferred conformation of the six-membered chair-like cyclic transition state will be strongly dictated by an equatorial position of the β-lactam nucleus and the phenyl ring. In this manner the *anti* product **13** will preferentially be formed. For crotylzinc bromide, the conformational preference in the transition state is much less outspoken, leading to a mixture of diastereomeric products derived from C_{11}. Also the steric size of the substituent at the aldehyde has an influence on the *anti/syn* ratio. This ratio increases with an increasing size of the aldehyde R-group.[6]

The relative stereochemistry at the hydroxyl bearing carbon atom will be governed by the facial selectivity of the reaction at the aldehyde function. In principle, the aldehyde (*e.g.* **1**) can react in four possible conformations (Figure 2). It was assumed

that the π-orbitals of the ester carbonyl, the C_3-C_4 double bond, and the formyl carbonyl have an optimal overlap (preferably a planar structure).

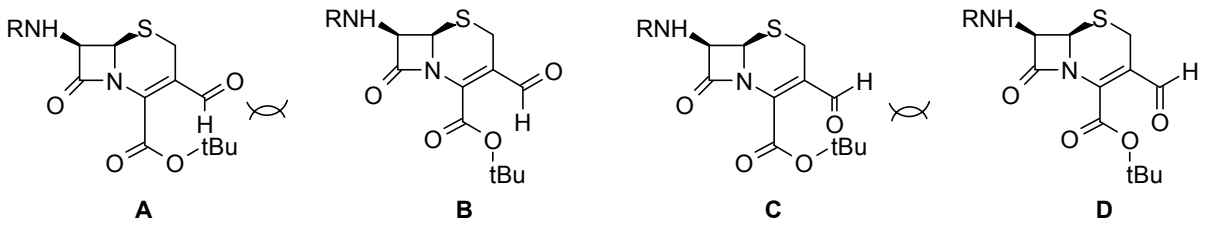


Figure 2.

Initially, a space-filling model was used to differentiate between the possible conformations. It is obvious that the bulky *tert*-butyl ester will escape from sterical hindrance, and therefore, the conformers **A** and **C** are energetically not very likely. However, using this simple model, it is more difficult to discriminate between conformers **B** and **D**. Therefore, information from an X-ray structure of aldehyde **1** was introduced in order to provide insight in this conformational preference. The result of this X-ray analysis is shown in Figure 3 and clearly reveals the s-trans conformation for the aldehyde moiety with respect to the olefinic bond, thus conformation **B**. It should be realized that this structural analysis refers to the solid state, however, it may be taken as strongly suggestive for the preference conformation in solution.

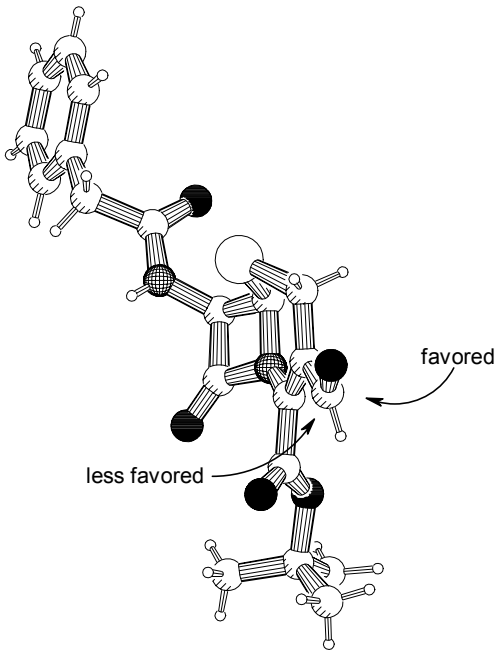


Figure 3. *PLUTON drawing of the X-ray structure of aldehyde* ***1****.*

In order to escape from sterical hindrance, the bulky *tert*-butyl ester will be slightly folded out of the plane. Assuming that conformation **B** predominates in solution, attack of the organozinc reagent from the least hindered face will be preferred. Such an attack leads to the stereochemistry at C_{10} as indicated in structure **13**. This structural assignment was substantiated by an X-ray analysis of two products. The two major isomers of products **14** and **17** did not gave suitable crystalline material for an diffraction analysis. Fortunately, the minor diastereomers of these products gave crystals which could be subjected to an X-ray structure analysis. The resulting structures are shown in Figure 4.

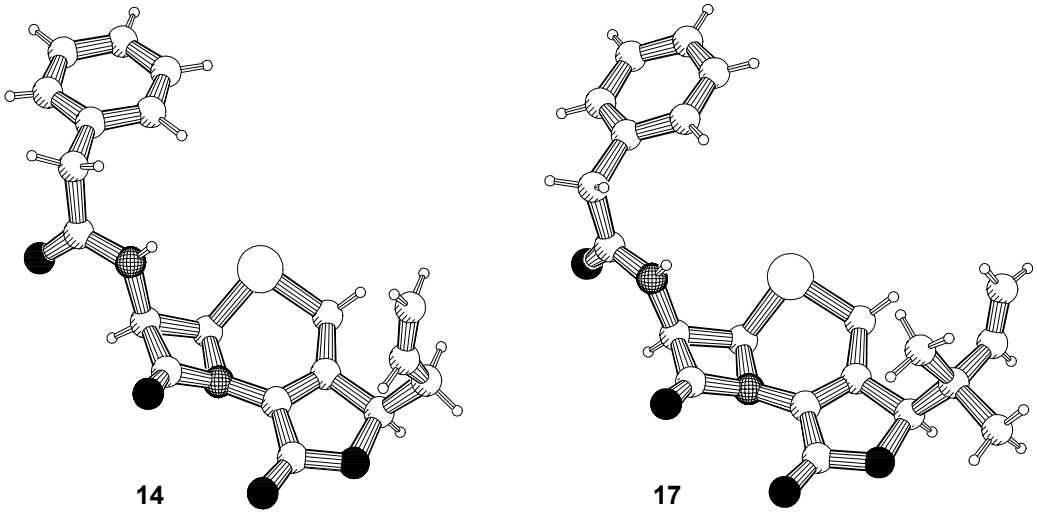


Figure 4. *PLUTON drawings of the X-ray structures of allyl lactone **14** and prenyl lactone **17** (minor isomers).*

The stereochemistry at C_{10} of the major isomers is opposite to that shown in Figure 4, and is pictured in Figure 5. These results are fully consistent with those derived from the face selectivity of the organozinc reaction. This face selectivity is clearly the result of steric approach control, which is governed by the spatial encumbrance of the folded nucleus.

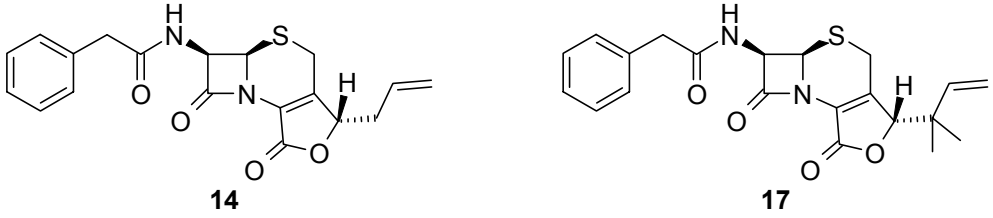
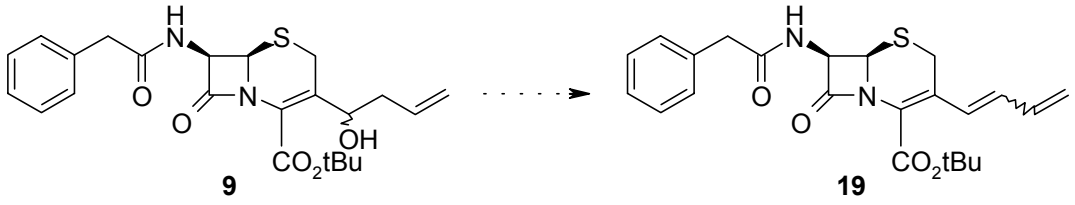


Figure 5. *Structures of the major diastereomers of lactones **14** and **17**.*

The high yields observed for the Barbier addition to the sensitive 3-formylcephalosporins show the relative mildness of this addition reaction. It may therefore be concluded that the Barbier addition offers unique opportunities to the selective functionalization of cephalosporins.

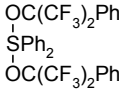
7.3 Some synthetic applications of allylated cephalosporins

In principle, the allylated cephalosporins are interesting building blocks for the preparation of new or existing antibiotics. The synthesis of cefprozil analogues **5** would be a nice illustration hereof. For this purpose, the synthesis of the vinyl analogues was attempted by dehydration of homoallyl alcohol **9** (Scheme 6). The results of the dehydration experiments are collected in Table 3.



Scheme 6.

Table 3: *Attempted dehydration of homoallylic alcohol* ***9****.*

entry:	conditions:	result:	yield (%):
1	*p*-TsOH, benzene, Dean-Stark, reflux	lactone **14**	n.d.[a]
2	pyridinium *p*-tosylate, 9 days	lactone **14**	62%
3	mesyl chloride, pyridine, -20°C	decomposition	-
4	Martin sulfurane dehydrating agent, -50°C 	**19**	44%[b]

[a] n.d. (not determined)

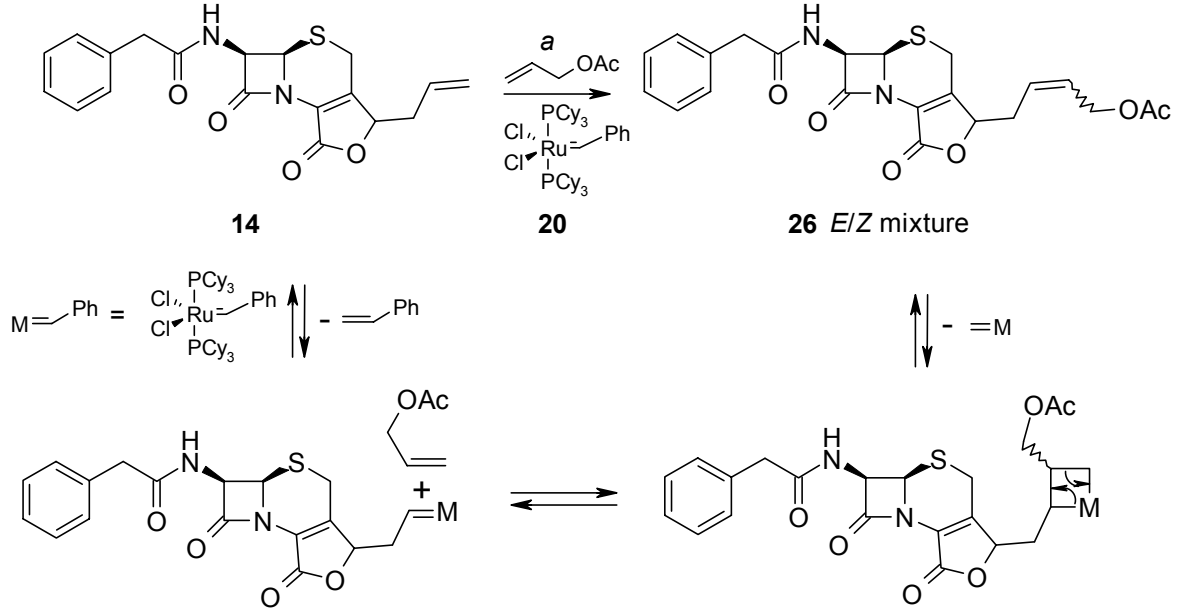
[b] as a mixture of *E*/*Z*, together with starting material **9**

Acid catalyzed dehydration of **9** with *p*-toluenesulfonic acid in toluene using a Dean-Stark apparatus (entry 1) did not lead to the desired conjugated alkene **19**. Instead, the allyllactone **14** (see Scheme 5) was formed. Apparently, intramolecular transesterification to lactone **14** had taken place under these acidic conditions. The

same lactone **14** was obtained in a yield of 62% by stirring alcohol **9** in dichloromethane in the presence of a catalytic amount of pyridinium *p*-tosylate[16] for 9 days (entry 2). It should be noted that only one epimeric alcohol **9** had undergone this lactonization reaction, as was indicated by the fact that a single lactone was obtained. No epimerization of the chiral center at C_{10} was observed.

Attempted conversion of the hydroxyl group of **9** into the corresponding mesylate by treatment with mesyl chloride in pyridine at -20°C only led to decomposition products (entry 3). Finally, Martin's sulfurane dehydration agent[17] was applied to enforce dehydration of homoallyl alcohol **9** (entry 4). After work-up without using water, the desired product **19** was obtained as an inseparable mixture of *E*- and *Z*-alkenes, together with some starting material. As product separation was not possible, no further attention was given to the synthesis of **19**.

For the purpose of synthetically modifying substrate **14**, a selective cross-methathesis[18],[19] with an olefin containing functional groups is an interesting application. Thus, a mixture of allyl lactone **14**, an excess of allyl acetate and Grubb's catalyst **20** was dissolved in dichloromethane and stirred at ambient temperature for 24 hours (Scheme 7). After work-up and purification, the expected metathesis product **26** was obtained as an inseparable mixture of *E*- and *Z*-alkenes, along with some self-metathesis products. The presence of acetoxy groups in both compounds in the complex reaction mixture was confirmed by ^{1}H-NMR (singlets at 2.05 and 2.06 ppm).



a) Grubb's catalyst **20**, *dichloroethane, 24h, 13%.*

Scheme 7.

This preliminary experiment only gave a modest yield of the desired products. However, employing different functionalized olefins and various types of Grubb's catalyst, including those belonging to the second generation, gives ample opportunities to improve this result. Such experiments could not be carried out due to time constraints.

7.4 Concluding remarks

The results described in this chapter clearly demonstrate that zinc mediated Barbier type additions to 3-formylcephalosporins are efficient and highly stereoselective reactions, which allow, depending on the nature of the ester moiety at C_4, the synthesis of a variety of 3-substituted homoallylic cephalosporins or the corresponding butenolides. The observed high diastereoselectivity can readily be explained by a steric approach control model by involving the hindrance of the β-lactam moiety.

Preliminary experiments suggest that further synthetic modifications of the allyl cephalosporins, *e.g.* by cross-metathesis, in order to obtain novel cephalosporin antibiotics, is a realistic option.

7.5 Experimental part

General remarks

100 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer and 300 MHz ^{1}H-NMR spectra and all ^{13}C-NMR spectra were recorded on a Bruker AC 300 using Me_4Si as internal standard. All coupling constants are given as ^{3}J in Hz, unless indicated otherwise. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Bio-Rad FTS-25 instrument. For mass spectra a double focusing VG7070E mass spectrometer was used. For some samples, High Resolution FAB was carried out using a JEOL JMS SX/SX102A four-sector mass spectrometer (JEOL Ltd. 1-2 Musashino 3-chome, Akishima Tokyo), coupled to a MS-MP 9021D/UPD data system (University of Amsterdam). Elemental analyses were conducted on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. For the determination of optical rotations a Perkin-Elmer 241MC polarimeter was used. Solvents were dried using the following methods: dichloromethane was distilled from P_2O_5; ethyl acetate was distilled from K_2CO_3; diethyl ether was distilled from NaH; hexane and heptane were distilled from CaH_2; tetrahydrofuran was distilled from sodium just before use. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on a Merck precoated silica gel 60 F254 plates (0.25 mm). Spots were visualized with

UV or using a molybdate spray. Flash chromatography was carried out at a pressure of *ca*. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was performed with ACROS silicagel (0.035-0.070 mm; pore diameter ca. 6 nm).
Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada).

General procedure for the organozinc addition reactions

Zinc dust (5 equiv.) and the corresponding bromide (2 equiv.) were added to a solution of aldehyde **1** or **2** in THF (10-20 ml)., Then, saturated aqueous ammonium chloride (5-10 ml) was added slowly at 0°C. After completion, the zinc salts were removed by filtration and ethyl acetate and 2N HCl were added to the filtrate. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography, followed by crystallization from ethyl acetate/heptane.

Benzhydryl (7*R*,7a*R*)-3-formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (2)

Aldehyde **2** was synthesized according to the procedure of Frigerio *et al*.[14] in 95% yield.
^{1}H-NMR (100 MHz, $CDCl_3$) δ (ppm) = 3.22 and 3.93 (qAB, J_{AB} = 18.4 Hz, 2H, SCH_2), 3.62 (s, 2H, $PhCH_2$), 4.98 (1H, *J* = 5.2 Hz, NHCHC*H*S), 5.96 (dd, *J* = 5.2 Hz *J* = 9.3 Hz, 1H, NHC*H*CHS), 6.24 (d, *J* = 9.3 Hz, 1H, NH), 7.05 (s, 1H, Ph_2CH), 7.20-7.34 (m, 15H, PhH and PhH (ester)), 9.62 (s, 1H, CHO); All other analytical data were in complete agreement with those reported previously.[20]

(1*R*) and (1*S*) *tert*-Butyl (7*R*,7a*R*)-3-[1-hydroxy-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (9)

The reaction was performed according to the general procedure, using aldehyde **1** (0.444 g; 1.10 mmol), allyl bromide (0.266 g; *ca*. 2 equiv.) and zinc dust (0.36 g; *ca*. 5 equiv.). After work-up, the crude mixture was purified by column chromatography (SiO_2, ethyl acetate / heptane 1:1) affording the allyl adducts **9** (0.430 g; 89%) as a mixture of diastereomers (ratio 10:90). Analytical samples were obtained by crystallization from ethyl acetate / heptane: off-white plates (fast-moving isomer) and colorless needles (slow-moving isomer).

Fast-moving minor isomer (1*R*)-9

Mp 128-130°C (dec.); $[\alpha]_D$ = +73.0° (c = 0.61; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.48 (s, 9H, $C(CH_3)_3$), 2.17-2.27 (mAB, 1H, $CH_2CH=CH_2$), 2.41-2.50 (mAB, 1H, $CH_2CH=CH_2$), 3.32 and 3.64 (qAB, J_{AB} = 17.9 Hz, 2H, SCH_2), 3.56 (s, 2H, $PhCH_2$), 3.51 (bs, 1H, OH), 4.87 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 4.90 (t, *J* = 7.5 Hz, 1H, C(OH)*H*CH_2), 5.05-5.11 (m, 2H, CH=CH_2), 5.57-5.69 (m, 1H, C*H*=CH_2), 5.74 (dd, *J* = 4.8 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 7.19-7.34 (m, 6H, PhH and NH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.6 (SCH_2), 27.7 ($C(CH_3)_3$), 38.0 ($CH_2CH=CH_2$), 43.3 ($PhCH_2$), 57.9 (CHNH), 58.8 (CHS), 68.4 (CHOH), 84.0 ($C(CH_3)_3$), 117.8 (CH=CH_2), 125.5 (=CCHOH), 127.3, 128.8, 129.4, and 134.0 (PhC), 129.6 (=$CCO_2{}^tBu$), 133.4 ($CH=CH_2$), 161.2 ($CO_2{}^tBu$), 165.1 (C=O, lactam), 171.4 ($PhCH_2C(O)$); IR (KBr): ν 3435 (broad, OH), 3272 (broad, NH), 1786 (C=O, lactam), 17157 (C=O, ester), 1688 and 1514 (C=O, amide), 1391 (C-N), 1156 (C-O, ester) cm^{-1}; MS (CI^+): *m/z* (%) = 474 (1) $[M+C_2H_5]^+$, 445 (1) $[M+H]^+$, 459 (1), $[M+H]^+$, 404 (1), 377 (2), 174 (15), 136 (6), 91 (19) $[PhCH_2{}^+]$, 57 (100) $[C_4H_9{}^+]$; HRMS (CI^+, m/z): calculated for $C_{23}H_{28}O_5N_2S$ $[M^+]$: 444.1719 amu. Found: 444.17183 ± 0.00133 amu.

Slow-moving major isomer (1*S*)-9

Mp 221-223°C (dec.); $[\alpha]_D$ = +10.0° (c = 0.13; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.50 (s, 9H, $C(CH_3)_3$), 2.25-2.35 (mAB, 1H, $CH_2CH=CH_2$), 2.44-2.52 (mAB, 1H, $CH_2CH=CH_2$), 2.80 (d, *J* = 3.6 Hz, 1H, CHO*H*), 3.40 and 3.52 (qAB, J_{AB} = 18.6 Hz, 2H, SCH_2), 3.62 (s, 2H, $PhCH_2$), 4.81-4.87 (m, 1H, C*H*OH), 4.88 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 5.14-5.19 (m, 2H, $CH=CH_2$), 5.75 (dd, *J* = 4.8 Hz *J* = 8.9 Hz, 1H, NHC*H*CHS), 5.78-5.92 (m, 1H, $CH=CH_2$), 6.58 (d, 8.9 Hz, 1H, NH), 7.24-7.38 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 24.5 (SCH_2), 27.7 ($C(CH_3)_3$), 40.4 ($CH_2CH=CH_2$), 43.1 ($PhCH_2$), 57.7 (CHNH), 58.8 (CHS), 69.6 (CHOH), 83.3 ($C(CH_3)_3$), 118.7 ($CH=CH_2$), 123.8 (=CCHOH), 127.5, 129.0, 129.2, and 133.7 (PhC), 133.0 (=CCO_2^{t}Bu), 133.8 ($CH=CH_2$), 160.7 (CO_2 ^{t}Bu), 164.3 (C=O, lactam), 171.4 ($PhCH_2C(O)$).

(1*R*) and (1*S*) *tert*-Butyl (7*R*,7a*R*)-3-[(1*S*)-1-hydroxy-3-butynyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (10)

Aldehyde **1** (0.805 g; 2.0 mmol) was treated according to the general procedure (propargyl bromide) to give, after column chromatography (SiO_2, ethyl acetate / heptane 1:1), both propargyl adducts **10** (0.708 g; 85%) as two separable diastereomers in a ratio of 10:90. Analytical samples were obtained by crystallization from ethyl acetate / heptane.

Fast-moving minor isomer (1*R*)-10

Mp 123-125°C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.50 (s, 9H, $C(CH_3)_3$), 1.98 (t, ^4J = 2.6 Hz, 1H, C≡CH), 2.41 (m (part of AB), J_{AB} = 17.7 Hz *J* = 9.2 Hz *J* = 2.6 Hz, 1H, $CHCH_2C{\equiv}CH$), 2.58 (m (part of AB), J_{AB} = 17.7 Hz *J* = 6.0 Hz *J* = 2.6 Hz, 1H, $CHCH_2C{\equiv}CH$), 3.43 and 3.63 (qAB, J_{AB} = 17.9 Hz, 2H, SCH_2), 3.56 and 3.58 (qAB, *J* = 15.7 Hz, 2H, $PhCH_2$), 3.72 (bs, 1H, OH), 4.91 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 5.04 (dd, *J* = 6.0 Hz *J* = 9.2, 1H, $CH(OH)CH_2$), 5.76 (dd, *J* = 4.8 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 7.13 (d, *J* = 9.2 Hz, 1H, NH), 7.20-7.34 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.2 ($CH_2C{\equiv}CH$), 23.8 (SCH_2), 27.8 ($C(CH_3)_3$), 43.4 ($PhCH_2$), 57.8 (CHNH), 58.9 (CHS), 67.5 (CHOH), 70.8 (C≡CH), 79.5 (C≡CH), 84.2 ($C(CH_3)_3$), 126.3 (=CCHOH), 127.3, 128.9, 129.4 and 133.9 (PhC), 128.5 (=CCO_2), 161.2 (CO_2 ^{t}Bu), 165.2 (C=O, lactam), 171.4 ($PhCH_2C(O)$); IR (KBr): ν 3418 (broad, OH), 3377 (broad, NH), 1771 (C=O, lactam), 1692 (C=O, ester), 1667 and 1538 (C=O, amide), 1365 (C-N), 1155 (C-O, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 443 (1), $[M+H]^+$, 425 (1) $[M+H-H_2O]^+$, 404 (1), 377(1) $[M+H-C_4H_8]^+$, 349 (1), 331 (1), 230 (8), 174 (15), 91 (16) $[PhCH_2^+]$, 57 (100) $[C_4H_9^+]$; HRMS (CI$^+$, m/z): calculated for $C_{23}H_{26}O_5N_2S$ $[M^+]$: 442.1562 amu. Found: 442.15617 ± 0.00133 amu.

Slow-moving major isomer (1*S*)-10

Mp 139-141°C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.50 (s, 9H, $C(CH_3)_3$), 2.12 (t, ^4J = 2.6 Hz, 1H, C≡CH), 2.55 (m (part of AB), J_{AB} = 16.7 Hz *J* = 7.9 Hz *J* = 2.6 Hz, 1H, $CHCH_2C{\equiv}CH$), 2.66 (m (part of AB), J_{AB} = 16.7 Hz *J* = 4.1 Hz *J* = 2.6 Hz, 1H, $CHCH_2C{\equiv}CH$), 3.13 (d, *J* = 3.9 Hz, 1H, OH), 3.57 (s, 2H, $PhCH_2$), 3.56 (s, 2H, SCH_2), 4.89 (d, *J* = 4.9 Hz, 1H, NHCHC*H*S), 4.88-4.95 (m, 1H, $CH(OH)CH_2$), 5.78 (dd, *J* = 4.9 Hz *J* = 8.9 Hz, 1H, NHC*H*CHS), 6.41 (d, *J* = 8.9 Hz, 1H, NH), 7.25-7.38 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 24.6 ($CH_2C{\equiv}CH$), 26.6 (SCH_2), 27.8 ($C(CH_3)_3$), 43.1 ($PhCH_2$), 57.5 (CHNH), 58.9 (CHS), 68.8 (CHOH), 71.7 (C≡CH), 80.1 (C≡CH), 83.6 ($C(CH_3)_3$), 124.4 (=CCHOH), 127.5, 129.0, 129.1 and 133.6 (PhC), 131.9 (=CCO_2), 160.6 (CO_2 ^{t}Bu), 164.4 (C=O, lactam), 171.3 ($PhCH_2C(O)$).

(1*R*,2*R*), (1*R*,2*S*), (1*S*,2*R*), and (1*S*,2*S*) *tert*-Butyl (7*R*,7a*R*)-3-[-1-hydroxy-2-methyl-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (11)

Aldehyde **1** (0.810 g; 2.01 mmol) was treated according to the general procedure (crotyl bromide) to give, after column chromatography (SiO_2, ethyl acetate / heptane 1:1), the adducts **11** (0.729 g; 79%) as two separable diastereomers (50:50 ratio), both containing an inseparable mixture of *syn* / *anti* isomers. Analytical samples were obtained by crystallization from ethyl acetate / heptane.

Fast-moving minor isomers (1*R*,2*S*)-11 and (1*R*,2*R*)-11 (ratio 5:2)

(1*R*,2*S*)-11: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 0.81 (d, *J* = 6.8 Hz, 1H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 2.25-2.35 (m, 1H, C*H*CH_3), 3.29 and 3.74 (qAB, J_{AB} = 17.8 Hz, 2H, SCH_2), 3.56 (s, 2H, $PhCH_2$), ~3.5 (bs, OH, 1H), 4.64 (d, *J* = 9.7 Hz, 1H, C*H*OH), 4.91 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.12 (d, *J* = 11.2 Hz, 1H, $CH{=}CH_tH_c$), 5.13 (d, *J* = 16.2 Hz, 1H, $CH{=}CH_tH_c$), 5.41-5.51 (m, 1H, C*H*OCH(CH_3)), 5.68-5.76 (m, 1H, NHC*H*CHS), 5.81 (d, *J* = 9.3 Hz, 1H, NH), 7.20-7.33 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 16.7 ($CHCH_3$), 22.5 (SCH_2), 27.8 ($C(CH_3)_3$), 41.4 ($CHCH_3$), 43.4 ($PhCH_2$), 58.2 (CHNH), 58.8 (CHS), 72.5 (CHOH), 83.9 ($C(CH_3)_3$), 115.7 ($CH{=}CH_2$), 125.8 (=CCHOH), 127.3, 128.9, 129.4, and 133.9 (PhC), 139.4 (=$CCO_2{}^t$Bu), 140.9 ($CH{=}CH_2$), 162.5 ($CO_2{}^t$Bu), 165.0 (C=O, lactam), 171.6 ($PhCH_2C$(O)); IR (KBr): ν 3449 (broad, OH), 3326 (broad, NH), 1757 (C=O, lactam), 1711 (C=O, ester), 1669 and 1536 (C=O, amide), 1368 (C-N), 1156 (C-O, ester) cm^{-1}; MS (CI$^+$): *m/z* (%) = 487 (1) [M+C_2H_5]$^+$, 459 (1), [M+H]$^+$, 403 (4) [M+H-C_4H_8]$^+$, 385 (16), 347 (12), 210 (27), 194 (15), 136 (10), 91 (60) [$PhCH_2^+$], 57 (100) [$C_4H_9^+$].

(1*R*,2*R*)-11:^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.13 (d, *J* = 6.4 Hz, 1H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 1.90-2.05 (m, 1H, C*H*CH_3), 3.50-3.69 (qAB, J_{AB} = 18.0 Hz, 2H, SCH_2), 3.56 (s, 2H, $PhCH_2$), ~3.5 (bs, OH, 1H), 4.59 (d, *J* = 9.7 Hz, 1H, C*H*OH), 4.85 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 4.90-5.05 (m, $CH{=}CH_tH_c$), 5.41-5.51 (m, 1H, C*H*OCH(CH_3)), 5.68-5.76 (m, 1H, NHC*H*CHS), 5.87 (d, *J* = 9.3 Hz, 1H, NH), 7.20-7.33 (m, 5H, PhH).

Slow-moving major isomers (1*S*,2*R*)-11 and (1*S*,2*S*)-11 (ratio 7:3)

(1*S*,2*R*)-11: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.11 (d, *J* = 6.6 Hz, 1H, CH_3), 1.50 (s, 9H, $C(CH_3)_3$), 2.50-2.55 (m, 1H, C*H*CH_3), 3.37 and 3.48 (qAB, J_{AB} = 18.5 Hz, 2H, SCH_2), 3.62 (s, 2H, $PhCH_2$), ~3.6 (bs, OH, 1H), 4.46 (d, *J* = 7.3 Hz, 1H, C*H*OH), 4.89 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 4.96-5.19 (m, 3H, C*H*=CH_2), 5.71-5.80 (m, 2H, C*H*OCH(CH_3) and NHC*H*CHS), 6.31 (d, *J* = 9.0 Hz, 1H, NH), 7.25-7.38 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 16.1 ($CHCH_3$), 25.6 (SCH_2), 27.8 ($C(CH_3)_3$), 43.3 ($CHCH_3$)*, 44.2 ($PhCH_2$)*, 57.7 (CHNH), 58.9 (CHS), 74.8 (CHOH), 83.4 ($C(CH_3)_3$), 115.7 ($CH{=}CH_2$), 125.1 (=CCHOH), 127.6, 129.1, 129.4, and 133.8 (PhC), 139.7 ($CH{=}CH_2$), 140.3 (=$CCO_2{}^t$Bu), 161.5 $CO_2{}^t$Bu), 164.4 (C=O, lactam), 171.3 ($PhCH_2C$(O)) (*: signals may have interchanged).

(1*S*,2*S*)-11: ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.00 (d, *J* = 6.9 Hz, 1H, CH_3), 1.50 (s, 9H, $C(CH_3)_3$), 2.40-2.45 (m, 1H, C*H*CH_3), 3.40-3.56 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 3.62 (s, 2H, $PhCH_2$), ~3.6 (bs, OH, 1H), 4.67 (d, *J* = 7.6 Hz, 1H, C*H*OH), 4.94 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 4.96-5.19 (m, 3H, C*H*=CH_2), 5.71-5.80 (m, 2H, C*H*OCH(CH_3) and NHC*H*CHS), 6.24 (d, *J* = 9.0 Hz, 1H, NH), 7.25-7.38 (m, 5H, PhH).

(1*R*) and (1*S*) *tert*-Butyl (7*R*,7a*R*)-3-[1-hydroxy-2,2-dimethyl-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (12)

Prenyl adducts **12** were synthesized from aldehyde **1** (0.750 g; 1.86 mmol) according to the general procedure (prenyl bromide). After column chromatography (SiO_2, ethyl acetate / heptane 4:6), adducts **12** (0.698 g; 80%) were obtained in a diasteromeric ratio of 33:67. Analytical samples were obtained by crystallization from ethyl acetate / heptane: colorless plates (fast-moving isomer) and colorless needles (slow-moving isomer).

Fast-moving minor isomer (1*R*)-12

Mp 170-172°C (dec.); $[\alpha]_D$ = +52.0° (c = 0.46; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 0.96 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$), 3.22 (d, *J* = 3.2 Hz, 1H, OH), 3.29 and 3.67 (qAB, J_{AB} = 17.6 Hz, 2H, SCH_2), 3.56 (s, 2H, $PhCH_2$), 4.93 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 4.95-5.04 (m, 3H, CH=CH_2 and C*H*OH), 5.71 (dd, *J* = 4.7 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 6.02 (dd, *J* = 17.4 Hz *J* = 11.0 Hz, 1H, C*H*=CH_tH_c), 7.12 (d, *J* = 9.2 Hz, 1H, NH), 7.20-7.34 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.9 $(CH_3)^*$, 25.9 $(CH_3)^*$, 23.8 $(SCH_2)^*$, 27.8 (C(*C*$H_3)_3$), 42.0 (*C*HCH_3), 43.4 ($PhCH_2$), 58.7 (CHNH)#, 58.9 (CHS)#, 75.1 (CHOH), 83.8 (*C*$(CH_3)_3$), 112.7 (CH=*C*H_2), 125.8 (=*C*CHOH), 127.3, 128.9, 129.4, and 134.0 (PhC), 130.1 (=*C*$CO_2{}^t$Bu), 144.3 (*C*H=CH_2), 161.5 (*C*$O_2{}^t$Bu), 165.3 (C=O, lactam), 171.4 ($PhCH_2$*C*(O)) (*,#: signals may have interchanged); IR (KBr): ν 3415 (broad, OH), 3292 (broad, NH), 1775 (C=O, lactam), 1717 (C=O, ester), 1668 and 1539 (C=O, amide), 1368 (C-N), 1153 (C-O, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 495 (2) $[M+Na]^+$, 473 (1) $[M+H]^+$, 439 (1) $[M+Na-C_4H_8]^+$, 413 (2) $[M+H-C_4H_8]^+$, 399 (5), 298 (7), 253 (20), 242 (39), 224 (55), 176 (93), 91 (100) [$PhCH_2^+$], 57 (95) [$C_4H_9^+$]; HRMS (FAB, m/z): calculated for $C_{25}H_{33}O_5N_2S^+$: 473.2110 amu. Found: 473.2141 ± 0.0047 amu.

Slow-moving major isomer (1*S*)-12

Mp 213-215°C (dec.); $[\alpha]_D$ = +69.4° (c = 0.89; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.04 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.50 (s, 9H, $C(CH_3)_3$), 3.24 (d, *J* = 5.6 Hz, 1H, OH), 3.36 and 3.40 (qAB, J_{AB} = 17.1 Hz, 2H, SCH_2), 3.61 (s, 2H, $PhCH_2$), 4.81 (d, *J* = 5.6 Hz, 1H, C*H*OH), 4.89 (d, *J* = 4.7 Hz, 1H, NHCHC*H*S), 5.04 (d, *J* = 17.6 Hz, 1H, CH=CH_cH_t), 5.08 (d, *J* = 10.8 Hz, 1H, CH=CH_cH_t), 5.66 (dd, *J* = 4.7 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 6.05 (dd, *J* = 17.6 Hz *J* = 10.8 Hz, 1H, C*H*=CH_tH_c), 6.55 (d, *J* = 8.7 Hz, 1H, NH), 7.25-7.36 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.6 $(CH_3)^*$, 25.9 $(CH_3)^*$, 26.2 $(SCH_2)^*$, 27.7 (C(*C*$H_3)_3$), 42.5 (*C*HCH_3), 43.1 ($PhCH_2$), 58.5 (CHNH)#, 59.2 (CHS)#, 76.6 (CHOH), 83.4 (*C*$(CH_3)_3$), 113.6 (CH=*C*H_2), 126.0 (=*C*CHOH), 127.4, 128.9, 129.3, and 133.8 (PhC), 136.9 (=*C*$CO_2{}^t$Bu), 144.3 (*C*H=CH_2), 161.2 (*C*$O_2{}^t$Bu), 164.6 (C=O, lactam), 171.3 ($PhCH_2$*C*(O)) (*,#: signals may have interchanged).

***tert*-Butyl (7*R*,7a*R*)-3-[(1*S*,2*R*)-1-hydroxy-2-phenyl-3-butenyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (13)**

Aldehyde **1** (0.810 g; 2.01 mmol) was reacted with cinnamyl bromide according to the general procedure to give, after column chromatography (SiO_2, ethyl acetate / heptane 1:1), adduct **13** (0.743 g; 71%) as one single stereoisomer. An analytical sample was obtained by crystallization from ethyl acetate / heptane.

Mp 87-90°C (dec.); $[\alpha]_D$ = +46.9° (c = 1.02; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.45 (s, 9H, $C(CH_3)_3$), 3.18 and 3.68 (qAB, J_{AB} = 17.7 Hz, 2H, SCH_2), 3.38-3.54 (m, 1H, C*H*Ph), 3.46 and 3.51 (qAB, J_{AB} = 15.6 Hz, 2H, $PhCH_2$), 3.63 (d, *J* = 2.0 Hz, 1H, OH), 4.47 (d, *J* = 4.8 Hz, 1H, NHCHC*H*S), 5.03 (d, *J* = 17.0 Hz, 1H, CH=CH_tH_c), 5.16 (d, *J* = 10.3 Hz, 1H, CH=CH_tH_c), 5.27 (dd, *J* = 10.4 Hz *J* = 1.6 Hz, 1H, C*H*OH), 5.53 (dd, *J* = 4.8 Hz *J* = 9.2 Hz, 1H, NHC*H*CHS), 7.05 (d, *J* = 9.2 Hz, 1H, NH), 6.99-7.36 (m, 10H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.7 (SCH_2), 27.8 (C(*C*$H_3)_3$), 43.4 ($PhCH_2$), 54.0 (*C*HPh), 57.8 (CHNH), 68.9 (CHS), 71.3 (CHOH), 83.7 (*C*$(CH_3)_3$), 116.9 (=CH_2), 126.1 (=*C*CHO), 125.9, 127.0, 127.3, 127.7, 128.0, 128.5, 128.7, 128.8, 128.9, 129.4, 133.8 (PhC, CHPh*C*H=CH_2, =*C*CO_2CH), 139.2 (*C*H=CH_2), 140.0 (=*C*$CO_2{}^t$Bu), 160.9 (*C*$O_2{}^t$Bu), 164.7 (C=O, lactam), 171.3 ($PhCH_2$*C*(O)); IR (KBr): ν 3508 (broad, OH), 3310 (broad, NH), 1775 (C=O, lactam), 1713 (C=O, ester), 1665 and 1537 (C=O, amide), 1368 (C-N), 1154 (C-O, ester) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 543 (2) $[M+Na]^+$, 521 (2) $[M+H]^+$, 463 (3) $[M+H-C_4H_8]^+$, 447 (9) $[M+H-C_4H_8-H_2O]^+$, 347 (10), 290 (18), 272 (39), 176 (100), 154 (45)

[NOBA]*, 136 (54), 91 (67) [$PhCH_2^+$] (* defragmentation of NOBA matrix); HRMS (FAB, m/z): calculated for $C_{29}H_{32}O_5N_2SNa^+$: 543.1930 amu. Found: 543.1917 ± 0.0054 amu.; HRMS (FAB, m/z): calculated for $C_{29}H_{32}O_5N_2SNa^+$ [M-H_2O]$^+$: 503.2005 amu. Found: 503.2037 ± 0.0050 amu.

(3*S*) and (3*R*) *N*1-[(5a*R*,6*R*)-3-Allyl-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (14)

Aldehyde **2** (0.77 g; 1.5 mmol) was converted in the corresponding allyl-lactones **14** according to the general procedure (allyl bromide). After column chromatography (SiO_2, ethyl acetate / heptane 4:6) and crystallization from ethyl acetate / heptane, lactones **14** (0.423 g; 76%) were obtained as a white solid (fast-moving isomer) and colorless needles (slow-moving isomer) in a ratio of 80:20.

Fast-moving major isomer (3*S*)-14

Mp 188-190°C (dec.); $[\alpha]_D$ = +89.1° (c = 0.53; acetone); ^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm) = 2.49-2.59 (mAB, 1H, C*H*$_2$CH=CH$_2$), 2.73-2.82 (mAB, 1H, C*H*$_2$CH=CH$_2$), 3.68 and 3.73 (qAB, J_{AB} = 14.4 Hz, 2H, $PhCH_2$), 3.77 and 3.90 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 5.16 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.16-5.30 (m, 2H, =CH_2), 5.33 (t, *J* = 5.2 Hz, 1H, OC*H*CH_2), 5.74-5.86 (m, 1H, C*H*=CH_2), 6.00 (dd, *J* = 5.0 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 7.29-7.42 (m, 5H, PhH), 8.13 (d, *J* = 8.7 Hz, 1H, NH); ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm) = 23.3 (SCH_2), 37.1 (*C*H_2CH=CH_2), 42.9 ($PhCH_2$), 58.4 (CHNH), 60.9 (CHS), 82.2 (O*C*HCHCH$_3$), 119.8 (=CH_2), 125.4 (=*C*CHO), 127.5, 129.1, 130.0, and 136.4 (PhC), 132.1 (*C*H=CH_2), 143.2 (=*C*CO_2), 164.9 (C=O, lactam), 166.2 (*C*O_2CH_2), 171.6 ($PhCH_2$*C*(O)); IR (KBr): ν 3258 (broad, NH), 1787 (C=O, lactam), 1760 (C=O, lactone), 1667 and 1546 (C=O, amide), 1412 (C-N), 1156 (C-O, lactone) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 393 (65) [M+Na]$^+$, 371 (64) [M+H]$^+$, 196 (22), 176 (48), 154 (100) [NOBA]*, 91 (22) [$PhCH_2^+$] (* defragmentation of NOBA matrix); HRMS (FAB, m/z): calculated for $C_{19}H_{19}O_4N_2S^+$: 371.1066 amu. Found: 371.1096 ± 0.0037 amu.

Slow-moving minor isomer (3*R*)-14

Mp 215-217°C (dec.); $[\alpha]_D$ = +173.0° (c = 0.30; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$ and acetone-d_6) δ (ppm) = 2.41-2.50 (mAB, 1H, C*H*$_2$CH=CH$_2$), 2.70-2.79 (mAB, 1H, C*H*$_2$CH=CH$_2$), 3.56 and 3.73 (qAB, J_{AB} = 18.5 Hz, 2H, SCH_2), 3.60 and 3.65 (qAB, J_{AB} = 14.5 Hz, 2H, $PhCH_2$), 5.02 (d, *J* = 5.1 Hz, 1H, NHCHC*H*S), 5.06-5.18 (m, 3H, CH=C*H*$_2$ and OC*H*CH_2), 5.54-5.67 (m, 1H, C*H*=CH_2), 5.88 (dd, *J* = 5.0 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 7.16-7.31 (m, 5H, PhH), 7.64 (d, *J* = 8.7 Hz, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$ and acetone-d_6) δ (ppm) = 21.6 (SCH_2), 35.0 (*C*H_2CH=CH_2), 41.6 ($PhCH_2$), 56.8 (CHNH), 69.3 (CHS), 80.2 (O*C*HCHCH$_3$), 118.6 (=CH_2), 124.2 (=*C*CHO), 126.0, 127.6, 128.4, and 134.2 (PhC), 129.8 (*C*H=CH_2), 141.1 (=*C*CO_2), 163.0 (C=O, lactam), 164.7 (*C*O_2CH_2), 170.5 ($PhCH_2$*C*(O)); IR (KBr): ν 3278 (broad, NH), 1789 (C=O, lactam), 1764 (C=O, lactone), 1662 and 1536 (C=O, amide), 1422 (C-N), 1142 (C-O, lactone) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 393 (37) [M+Na]$^+$, 371 (28) [M+H]$^+$, 196 (9), 176 (31), 154 (100) [NOBA]*, 91 (18) [$PhCH_2^+$] (* defragmentation of NOBA matrix).

(3*R*) and (3*S*) *N*1-[(5a*R*,6*R*)-1,7-Dioxo-3-(2-propynyl)-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (15)

Aldehyde **2** (1.025 g; 2.0 mmol) was treated according to the general procedure (propargyl bromide) to give **15** (0.699 g; 95%) as colorless plates (fast-moving isomer) and traces of a yellowish solid (slow-moving isomer) after purification by column chromatography (SiO_2, ethyl acetate/heptane 2:1), and subsequent crystallization from ethyl acetate / heptane.

Fast-moving major isomer (3*S*)-15

Mp 212-214°C (dec.); $[\alpha]_D$ = +120.0° (c = 0.35; acetone); ^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm) = 2.67 (t, ^4J = 2.6 Hz, 1H, C≡CH), 2.95 and 3.06 (q(dd)AB, J_{AB} = 17.3 Hz J = 5.1 Hz J = 2.6 Hz, 2H, CHCH_2C≡CH), 3.77 and 3.82 (qAB, J_{AB} = 14.4 Hz, 2H, PhCH_2), 3.91 and 3.98 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 5.25 (d, J = 5.1 Hz, 1H, NHCHC*H*S), 5.48 (t, J = 5.1 Hz, 1H, OC*H*CH_2), 6.11 (dd, J = 5.1 Hz J = 8.6 Hz, 1H, NHC*H*CHS), 7.35-7.50 (m, 5H, PhH), 8.22 (d, J = 8.6 Hz, 1H, NH); ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm) = 23.2 (SCH_2 and *C*H_2C≡CH), 42.9 (PhCH_2), 58.4 (CHNH), 60.9 (CHS), 73.5 (C≡CH), 77.9 (*C*≡CH), 80.2 (OCHCH_2), 127.5, 129.2, 130.0, and 136.4 (PhC and =*C*CHO), 142.3 (=*C*CO_2), 165.0 (C=O, lactam), 165.9 (*C*O_2CH_2), 171.6 (PhCH_2*C*(O)); MS (CI$^+$): *m/z* (%) = 369 (3) [M+H]$^+$, 337 (5), 203 (30), 136 (66), 91 (100) [PhCH_2^+], 57 (52); HRMS (CI$^+$, m/z): calculated for $C_{19}H_{16}O_4N_2S$: 368.08310 amu. Found: 368.08238 ± 0.00110 amu.

Slow-moving minor isomer (3*R*)-15

Mp >150°C (slow dec.); $[\alpha]_D$ = +145.3° (c = 0.17; acetone); ^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm) = 2.54 (t, ^4J = 2.6 Hz, 1H, C≡CH), 2.92 and 3.05 (q(dd)AB, J_{AB} = 17.6 Hz J = 4.9 Hz J = 2.6 Hz, 2H, CHCH_2C≡CH), 3.71 and 3.76 (qAB, J_{AB} = 14.2 Hz, 2H, PhCH_2), 3.82 and 3.89 (qAB, J_{AB} = 18.6 Hz ^4J < 1.5 Hz, 2H, SCH_2), 5.17 (d, J = 5.1 Hz, 1H, NHCHC*H*S), 5.37 (t, J = 4.8 Hz, 1H, OC*H*CH_2), 6.03 (dd, J = 5.1 Hz J = 8.8 Hz, 1H, NHC*H*CHS), 7.27-7.43 (m, 5H, PhH), 8.17 (d, J = 8.8 Hz, 1H, NH); ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm) = 22.7 (*C*H_2C≡CH)*, 23.0 (SCH_2)*, 42.9 (PhCH_2), 58.2 (CHNH), 60.8 (CHS), 73.5 (C≡*C*H), 77.9 (*C*≡CH), 79.9 (OCHCH_2), 127.5, 129.1, 130.0, and 136.5 (PhC), 127.3 (=*C*CHO), 142.5 (=*C*CO_2), 164.9 (C=O, lactam), 166.0 (*C*O_2CH_2), 171.6 (PhCH_2*C*(O)) (*: signals may have interchanged).

(1*R*, 3*R*), (1*R*, 3*S*), (1*S*, 3*R*), and (1*S*, 3*S*) *N*1-(5a*R*,6*R*)-3-[1-Methyl-2-propenyl]-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl-2-phenylacetamide (16)

Aldehyde **2** (0.50 g; 0.975 mmol) was treated according to the general procedure (crotyl bromide) to give, after column chromatography (SiO_2, ethyl acetate/heptane 2:1) and crystallization from heptane/ethyl acetate, lactones **16** (0.275 g; 73%) as an inseparable mixture consisting of 2 isomers (ratio 4:3).

Major isomer 16

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.06 (d, J = 6.9 Hz, 3H, CH_3), 2.55 (m, 1H, C*H*CH_3), 3.35 and 3.59 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 3.61 and 3.65 (qAB, J_{AB} = 16.0 Hz, 2H, PhCH_2), 4.92 (d, J = 5.0 Hz, 1H, NHCHC*H*S), 4.96 (d, J = 5.1 Hz, 1H, OC*H*CHCH_3), 5.14 (d, J = 17.3 Hz, 1H, CH=CH_tH$_c$), 5.21 (d, J = 10.0 Hz, 1H, CH=CH_t*H*$_c$), 5.69-5.80 (m, 1H, C*H*=CH_tH$_c$), 5.90 (dd, J = 5.0 Hz J = 8.9 Hz, 1H, NHC*H*CHS), 6.44 (d, J = 8.9 Hz, 1H, NH), 7.24-7.37 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 14.9 (CH_3), 23.7 (SCH_2), 41.3 (*C*HCH_3), 43.2 (PhCH_2), 57.7 (CHNH), 60.0 (CHS), 85.7 (OCHCHCH_3), 117.8 (=CH_2), 125.5 (=*C*CHO), 127.7, 129.1, 129.5, and 137.1 (PhC), 139.7 (=*C*CO_2), 163.8 (C=O, lactam), 165.5 (*C*O_2CH), 171.3 (PhCH_2*C*(O)); IR (both isomers, KBr): ν 3385 (broad, NH), 1765 (broad, C=O, lactam and lactone), 1662, 1679 and 1505 (C=O, amide), 1423 (C-N), 1157 (C-O, lactone) cm^{-1}; MS (FAB$^+$, NOBA): *m/z* (%) = 407 (9) [M+Na]$^+$, 385 (36), 210 (62), 176 (100), 154 (54), [NOBA$^+$], 91 (58) [PhCH_2^+]; HRMS (FAB, m/z): calculated for $C_{20}H_{21}O_4N_2S^+$: 385.1222 amu. Found: 385.1237 ± 0.0039 amu.

Minor isomer 16

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.16 (d, J = 6.9 Hz, 3H, CH_3), 2.73 (m, 1H, C*H*CH_3), 3.34 and 3.54 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 3.61 and 3.65 (qAB, J_{AB} = 16.0 Hz, 2H, PhCH_2), 4.92 (d, J = 5.0 Hz, 1H, NHCHC*H*S), 4.96 (d, J = 5.1 Hz, 1H, OC*H*CHCH_3), 5.14 (d, J = 17.3 Hz, 1H, CH=CH_tH$_c$), 5.21 (d, J

= 10.0 Hz, 1H, CH=CH$_t$*H$_c$*), 5.53-5.65 (m, 1H, C*H*=CH$_t$H$_c$), 5.90 (dd, *J* = 5.0 Hz *J* = 8.9 Hz, 1H, NHC*H*CHS), 6.44 (d, *J* = 8.9 Hz, 1H, NH), 7.24-7.37 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 15.2 (CH_3), 23.3 (SCH_2), 40.0 (*C*HCH_3), 43.2 ($PhCH_2$), 57.5 (CHNH), 60.0 (CHS), 85.6 (O*C*HCHCH_3), 118.2 (=CH_2), 125.4 (=*C*CHO), 127.7, 129.1, 129.5, and 137.1 (PhC), 139.9 (=*C*CO_2), 163.8 (C=O, lactam), 165.7 (*C*O_2CH), 171.3 ($PhCH_2$*C*(O)).

(3*R*) and (3*S*) *N*1-[(5a*R*,6*R*)-3-(1,1-dimethylallyl)-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (17)

Aldehyde **2** (1.025 g; 2.0 mmol) was treated according to the general procedure (prenyl bromide) to give, after column chromatography (SiO_2, ethyl acetate/heptane 2:1), lactones **17** (0.606 g; 87%) as a 70:30 mixture of 2 diastereomers. Analytical samples were obtained by crystallization from ethyl acetate / heptane: white solid (fast-moving isomer) and transparent cubic crystals (slow-moving isomer).

Fast-moving major isomer (3*R*)-17

Mp 222-224°C (dec.); $[\alpha]_D$ = +84.0° (c = 0.53; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 0.97 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 3.31 and 3.52 (qAB, J_{AB} = 18.3 Hz, 2H, SCH_2), 3.59 (s, 2H, $PhCH_2$), 4.80 (s, 1H, CHOC), 4.92 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.16 (d, *J* = 17.3 Hz, 1H, CH=C*H$_t$*H$_c$), 5.17 (d, *J* = 10.7 Hz, 1H, CH=CH$_t$*H$_c$*), 5.80 (dd, *J* = 17.3 Hz *J* = 10.7 Hz, 1H, C*H*=CH$_t$H$_c$), 5.87 (dd, *J* = 5.0 Hz *J* = 8.8 Hz, 1H, NHC*H*CHS), 6.90 (d, *J* = 8.8 Hz, 1H, NH), 7.23-7.34 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 19.8 (CH_3), 25.0 (CH_3)*, 25.1 (SCH_2)*, 41.3 (*C*$(CH_3)_2$), 42.9 ($PhCH_2$), 57.7 (CHNH), 59.9 (CHS), 88.9 (O*C*HC$(CH_3)_2$), 115.5 (=CH_2), 125.6 (=*C*CHO), 127.4, 128.9, 129.4, and 134.0 (PhC), 139.5 (=*C*CO_2), 141.4 (*C*H=CH_2), 163.8 (C=O, lactam), 166.0 (*C*O_2CH), 171.5 ($PhCH_2$*C*(O)) (*: signals may have interchanged).

Slow-moving minor isomer (3*S*)-17

Mp 207-209°C (dec.); $[\alpha]_D$ = +144.6° (c = 0.18; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 0.94 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 3.52 and 3.75 (qAB, J_{AB} = 18.3 Hz *J* < 1.5 Hz, 2H, SCH_2), 3.63 and 3.67 (qAB, J_{AB} = 16.1 Hz, 2H, $PhCH_2$), 4.86 (s, 1H, CHOC), 4.95 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.24 (d, *J* = 17.5 Hz, 1H, CH=C*H$_t$*H$_c$), 5.28 (d, *J* = 10.7 Hz, 1H, CH=CH$_t$*H$_c$*), 5.91 (dd, *J* = 17.5 Hz *J* = 10.7 Hz, 1H, C*H*=CH$_t$H$_c$), 5.97 (dd, *J* = 5.0 Hz *J* = 8.8 Hz, 1H, NHC*H*CHS), 6.20 (d, *J* = 8.8 Hz, 1H, NH), 7.30-7.41 (m, 5H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 18.8 (CH_3), 23.9 (CH_3)*, 27.2 (SCH_2)*, 41.3 (*C*$(CH_3)_2$), 43.3 ($PhCH_2$), 57.0 (CHNH), 60.3 (CHS), 87.8 (O*C*HC$(CH_3)_2$), 115.5 (=CH_2), 128.5 (=*C*CHO), 127.8, 129.2, 129.5, and 133.5 (PhC), 140.8 (=*C*CO_2), 142.8 (*C*H=CH_2), 163.7 (C=O, lactam), 166.0 (*C*O_2CH), 171.2 ($PhCH_2$*C*(O)) (*: signals may have interchanged); IR (KBr): ν 3248 (broad, NH), 1770 (C=O (broad), lactam and ester), 1654 and 1554 (C=O, amide), 1415 (C-N) cm^{-1}; MS (CI^+): *m/z* (%) = 399 (17) $[M+H]^+$, 367 (15), 224 (38), 176 (45), 136 (37), 91 (100) [$PhCH_2^+$]; HRMS (CI^+, m/z): calculated for $C_{21}H_{22}O_4N_2S$ [M^+]: 398.1300 amu. Found: 398.13026 ± 0.00119 amu.

***N*1-(3*S*,5a*R*,6*R*)-1,7-Dioxo-3-[(1*S*)-1-phenyl-2-propenyl]-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl-2-phenylacetamide (18)**

Aldehyde **2** (1.025 g; 2.0 mmol) was treated according to the general procedure (cinnamyl bromide) yielding, after column chromatography (SiO_2, ethyl acetate/ heptane 2:1) and crystallization from ethyl acetate / heptane, lactone **18** (0.631 g; 70%) as colorless plates.

Mp 101-103°C (dec.); $[\alpha]_D$ = +200.7° (c = 0.28; acetone); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 3.00 and 3.44 (qAB, J_{AB} = 18.4 Hz ^5J <1.5 Hz, 2H, SCH_2), 3.60 (m, 1H, PhC*H*CH=), 3.63 and 3.65 (qAB, J_{AB} = 14.5 Hz, 2H, $PhCH_2$), 4.93 (d, *J* = 5.0 Hz, 1H, NHCHC*H*S), 5.07 (d, *J* = 17.1 Hz, 1H, CH=C*H$_t$*H$_c$), 5.20 (d, *J* =

10.3 Hz, 1H, CH=CH$_t$*H$_c$*), 5.29 (d, *J* = 4.5 Hz, 1H, OC*H*CHPh), 5.92 (dd, *J* = 5.0 Hz *J* = 8.7 Hz, 1H, NHC*H*CHS), 5.90-6.00 (m, 1H, C*H*=CH$_t$H$_c$), 6.11 (d, *J* = 8.7 Hz, 1H, NH), 7.29-7.41 (m, 10H, PhH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) = 23.0 (SCH_2), 43.3 ($PhCH_2$), 52.4 (CHPh), 57.3 (CHNH), 60.2 (CHS), 84.3 (OCHCHPh), 119.2 (=CH_2), 126.1 (=*C*CHO), 127.8, 128.0, 128.3, 129.2, 129.3, 129.5, 133.5 134.3, 138.3 and 140.2 (PhC, CHPh*C*H=CH_2, =*C*CO_2CH), 163.7 (C=O, lactam), 165.5 (*C*O_2CH), 171.0 ($PhCH_2$*C*(O)); IR (KBr): ν 3260 (broad, NH), 1795 (broad, C=O, lactam and lactone), 1670 and 1525 (C=O, amide), 1454 (C-N) cm^{-1}; MS (CI$^+$): *m/z* (%) = 447 (78) [M$^+$], 415 (71), 272 (100), 176 (76), 117 (44), 91 (45) [$PhCH_2^+$]; HRMS (CI$^+$, m/z): calculated for $C_{25}H_{22}O_4N_2S$: 446.13000 amu. Found: 446.13066 ± 0.00133 amu.

Dehydration experiment with allyl alcohol 9

To a solution of allyl alcohol **9** (0.10 g; 0.22 mmol) in chloroform (5 ml) Martin's dehydrating agent (0.142 g; 0.25 mmol) was added at -50°C and under a nitrogen atmosphere. The reaction was monitored by TLC analysis (ethyl acetate / heptane 1:1). After completion, the reaction mixture was concentrated to dryness under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, ethyl acetate/heptane 1:1), to afford **19** (0.044 g; 46%). ^{1}H-NMR showed **19** as a mixture of *E*- and *Z*-isomers, together with starting material **9**.

Metathesis with allyl lactone 14 employing Grubb's catalyst

Allyl lactone **14** (0.050 g; 0.13 mmol) was subjected to a metathesis reaction with allylacetate (0.1 ml) and Grubb's catalyst **20** (22.1 mg) in dichloroethane (5 ml) at room temperature. After 24h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, ethyl acetate/heptane 2:1), to afford **26** (8.0 mg; 13%) as an inseparable mixture of *E*- and *Z*-isomers (^{1}H-NMR analysis), indicated by the presence of olefinic protons (multiplets between 4.8 and 5.8 ppm).

7.6 Crystal structure data

(3*R*) *N*1-[(5a*R*,6*R*)-3-Allyl-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (14)

Crystals of **14** (slow-moving diastereomer) suitable for X-ray diffraction studies were obtained from heptane-ethyl acetate by diffusion. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, θ-2θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans) was applied.[21] The structure was solved by the program system DIRDIF[22] using the program PATTY[23] to locate the sulfur atom and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[24] with anisotropic parameters for the non-hydrogen atoms. All hydrogens, excepted the hydrogen attached to C(16), were initially placed at calculated positions and were freely refined subsequently. The hydrogen attached to C(16) was refined riding on the parent atom. A structure determination summary, a list of atom coordinates, a list of bond lengths and angles, a list of hydrogen coordinates, and a list of anisotropic displacement parameters are given in Table 4.

A PLUTON drawing[25] is shown in Figure 4.

Table 4: *Crystal data and structure refinement for compound **14** (slow-moving diastereomer)*

Crystal color	transparent colorless
Crystal shape	regular
Size [mm]	0.53 x 0.29 x 0.21 mm
Empirical formula	$C_{19}H_{18}N_2O_4S$
Molecular weight	370.41 g.mol^{-1}
Temperature	293(2) K
Radiation / wavelength	MoKα (graphite mon.) / 0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.6929(8) Å α = 90°
(25 reflections, 18.431 < θ < 21.309)	b = 11.8524(12) Å β = 90°
	c = 15.5755(11) Å γ = 90°
Volume	1789.4(3) Å^3
Z	4
Calculated density	1.375 Mg.m^{-3}
Absorption coefficient	0.208 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / θ-2θ
F(000)	776
θ-range for data collection	2.62 - 27.48°
Index ranges	0 ≤ h ≤ 12, 0 ≤ k ≤ 15, 0 ≤ l ≤ 20
Reflections collected / unique	2337 / 2337
Reflections observed	1830 ([$I_o > 2\sigma(I_o)$])
Absorption correction	Semi-empirical from ψ-scans
Range of rel. transm. factors	1.039 and 0.964
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	2337 / 0 / 303
Goodness-of-fit on F^2	1.054
SHELXL-97 weight parameters	0.091800 0.252700
Final R indices [I > 2σ(I)]	R_1 = 0.0517, wR_2 = 0.1303
R indices (all data)	R_1 = 0.0703, wR_2 = 0.1436
Largest difference peak and hole	0.483 and -0.325 e.Å^{-3}

(3*S*) *N*1-[(5a*R*,6*R*)-3-(1,1-dimethylallyl)-1,7-dioxo-1,4,6,7-tetrahydro-3*H*,5a*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl]-2-phenylacetamide (17)

Crystals of **17** (slow-moving diastereomer) suitable for X-ray diffraction studies were obtained from heptane-ethyl acetate. A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Mo-Kα radiation, Ω-scan mode. Unit cell dimensions were determined from the angular setting of 25

reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (ψ-scans)[21] was applied. The structure was solved by the program system DIRDIF[22] using the program PATTY[23] to locate the sulfur atom, and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97[24] with anisotropic parameters for the non-hydrogen atoms. All hydrogens were placed at calculated positions and were refined riding on the parent atoms. A structure determination summary, a list of atom coordinates, a list of bond lengths and angles, a list of hydrogen coordinates and a list of anisotropic displacement parameters are given in Table 5.
A PLUTON drawing[25] is shown in Figure 4.

Table 5: *Crystal data and structure refinement for compound **17** (slow-moving diastereomer)*

Crystal color	transparent colorless
Crystal shape	regular
Size [mm]	0.31 x 0.22 x 0.18 mm
Empirical formula	$C_{21}H_{22}N_2O_4S$
Molecular weight	398.47 g.mol^{-1}
Temperature	293(2) K
Radiation / wavelength	MoKα (graphite mon.) / 0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.1629(13) Å α = 90°
(25 reflections, 18.431 < θ < 21.309)	b = 12.237(3) Å β = 90°
	c = 18.108(3) Å γ = 90°
Volume	2030.4(6) Å^3
Z	4
Calculated density	1.304 Mg.m^{-3}
Absorption coefficient	0.188 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / Ω
F(000)	840
θ-range for data collection	3.00 - 27.49°
Index ranges	$0 \le h \le 11$, $-15 \le k \le 0$, $-23 \le l \le 0$
Reflections collected / unique	2630 / 2630
Reflections observed	1207 ($[I_o > 2\sigma(I_o)]$)
Absorption correction	Semi-empirical from ψ-scans
Range of rel. transm. factors	1.005 and 0.991
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	2260 / 0 / 255
Goodness-of-fit on F^2	1.084
SHELXL-97 weight parameters	0.038000 0.942500
Final R indices [I > 2σ(I)]	R_1 = 0.0724, wR_2 = 0.1119
R indices (all data)	R_1 = 0.1865, wR_2 = 0.1425
Largest difference peak and hole	0.281 and -0.240 e.Å^{-3}

7.7 References

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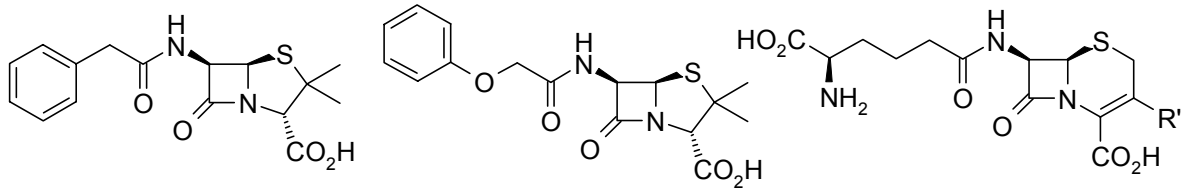
SUMMARY

The history of the life-saving β-lactam antibiotics started with the serendipitous discovery of penicillin G (**1**) by Alexander Fleming in 1928 (Figure 1). Important other milestones are the completion of the total synthesis of penicillin V (**2**) in 1957, and the discovery of the cephalosporins, *e.g.* cephalosporin C (**3**), a new family of β-lactam antibiotics with a broad-spectrum activity. This new class of β-lactams opened a new field of research aimed at the search for and exploration of more active anti-bacterial compounds. As a result, numerous new penicillins and cephalosporins were developed, of which several have successively been brought onto the market.



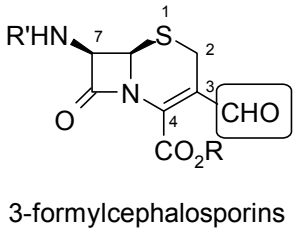
1 penicillin G **2** penicillin V **3** cephalosporin C

Figure 1.

Despite these successes, the worldwide incidence of antibiotic resistance among certain bacteria has increased. Therefore, much interest is still focused on the development of novel cephalosporin antibiotics in order to improve anti-bacterial activity against resistant bacterial strains. In this respect, the development of new synthetic methodologies and new reactions in the field of penicillin and cephalosporin chemistry is of extreme importance. This thesis deals with the syntheses of new β-lactam antibiotics from 3-formylcephalosporins as the key-intermediates (Figure 2). The research is mainly focused on the development of new synthetic methodologies and reactions for chemical transformations in cephalosporins. In view of the fact that 3-formylcephalosporins may become available from fermentation processes in the future, the chemistry concerning these 3-formyl derivatives falls well in the objectives of the cluster project "fine chemistry", which aims at clean, (bio)catalytic, efficient routes for β-lactam antibiotics.

In **Chapter 1**, relevant background information of the research is given. Attention is paid to the history of the β-lactam antibiotics, the mode of action of these anti-bacterial compounds, and the problem of increasing resistance of bacteria toward β-lactam antibiotics.

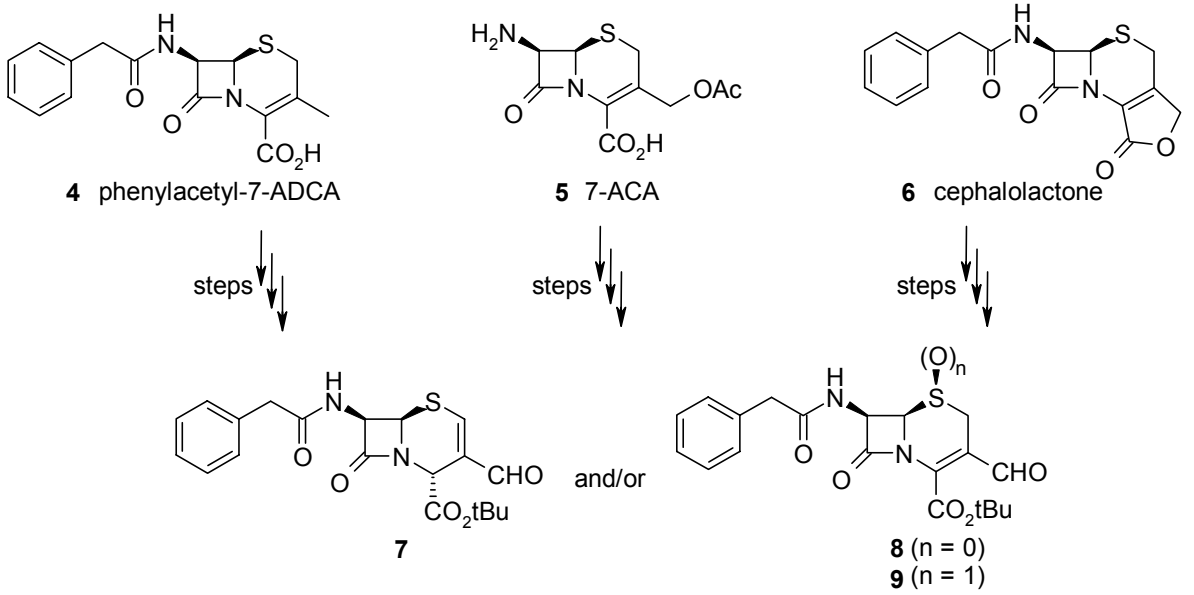
An overview of relevant literature of 3-formylcephalosporins is presented in **Chapter 2**. In this review, various aspects of the chemistry of 3-formylcephalosporins, the key-intermediates in this thesis, are covered. First, all reported syntheses of 3-formylcephalosporins are briefly summarized. The second part deals with applications and reactions of 3-formylcephalosporins. In this respect, the chemical behavior of the 3-formylgroup has been given special attention (Figure 2).



3-formylcephalosporins

Figure 2.

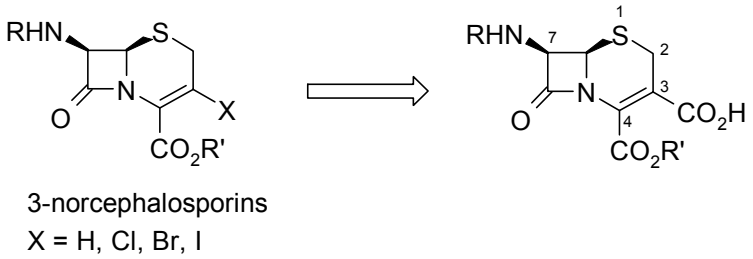
The development of a new and generally applicable synthetic methodology for the preparation of 3-formylcephalosporins from cheap and readily available starting materials, is described in **Chapter 3**. Starting from the phenylacetyl protected 7-aminodesacetylcephalosporanic acid, (7-phenylacetyl-ADCA) **4**, 7-amino-cephalosporanic acid (7-ACA) (**5**), and cephalolactone **6**, 3-formylcephalosporins **7-9** are synthesized in high overall yields (Scheme 1). Important aspects are the choice of the protecting groups, the chemical behavior in connection with the position of the double bond in the six-membered heteroatom ring, and the oxidation state of the sulfur atom.



Scheme 1.

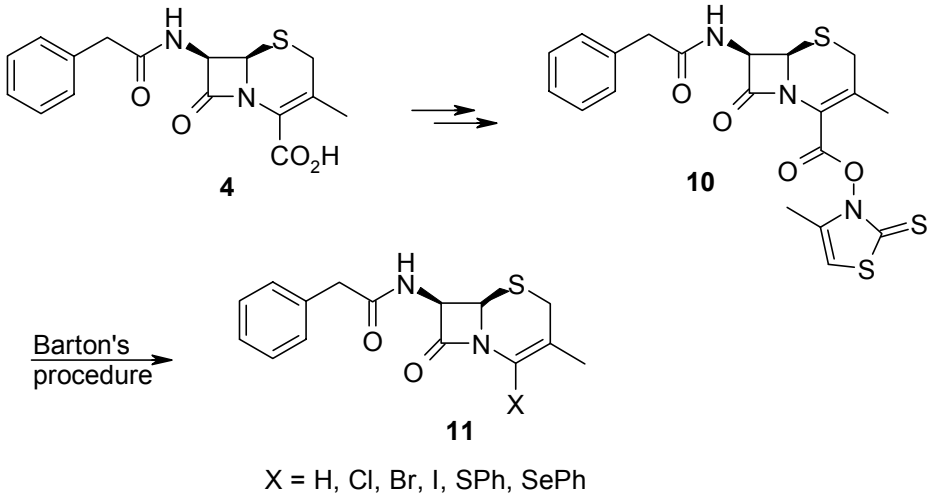
Although 7-phenylacetyl-ADCA **4** and cephalolactone **6** are suitable as starting material, the overall synthetic efficiency of the routes to 3-formylcephalosporins starting from these two compounds is inferior to that using 7-ACA (**5**).

In **Chapter 4**, a study towards the synthesis of 3-norcephalosporins is presented (Scheme 2).



Scheme 2.

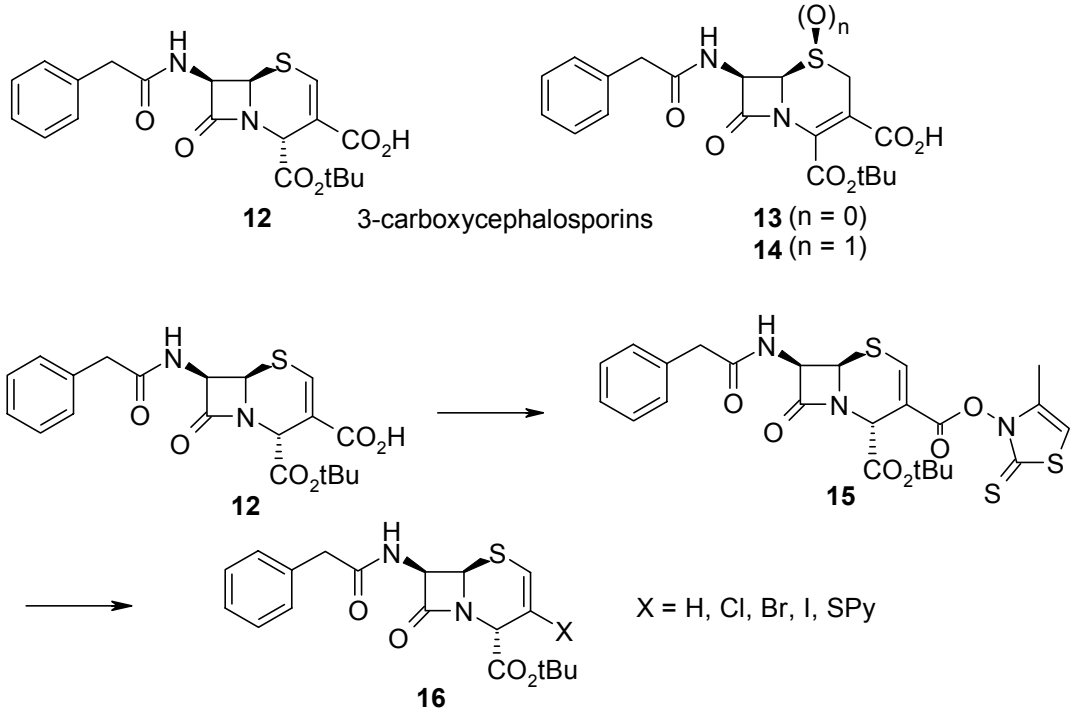
Non-radical as well as radical approaches to accomplish a (halo)-decarboxylation reaction on the model compound 7-phenylacetyl-ADCA **4** are described. Using Barton's radical decarboxylation reaction, a variety of 4-functionalized cephalosporins **11** has been synthesized *via* Barton ester **10** (Scheme 3). Moderate to good yields were obtained for the conversion of the carboxyl function into a hydrogen, chlorine, bromine or iodine substituent, as well as for the introduction of selenium- and sulfur-containing groups at the 4-position.



Scheme 3.

A new and improved method for the preparation of 3-carboxycephalosporins **12-14** from 3-formylcephalosporins has been developed (**Chapter 5**). These compounds can be used for further synthetic elaboration at C_3. As an example, 3-carboxycephalosporin **12-14** have been used as key-intermediates for a new

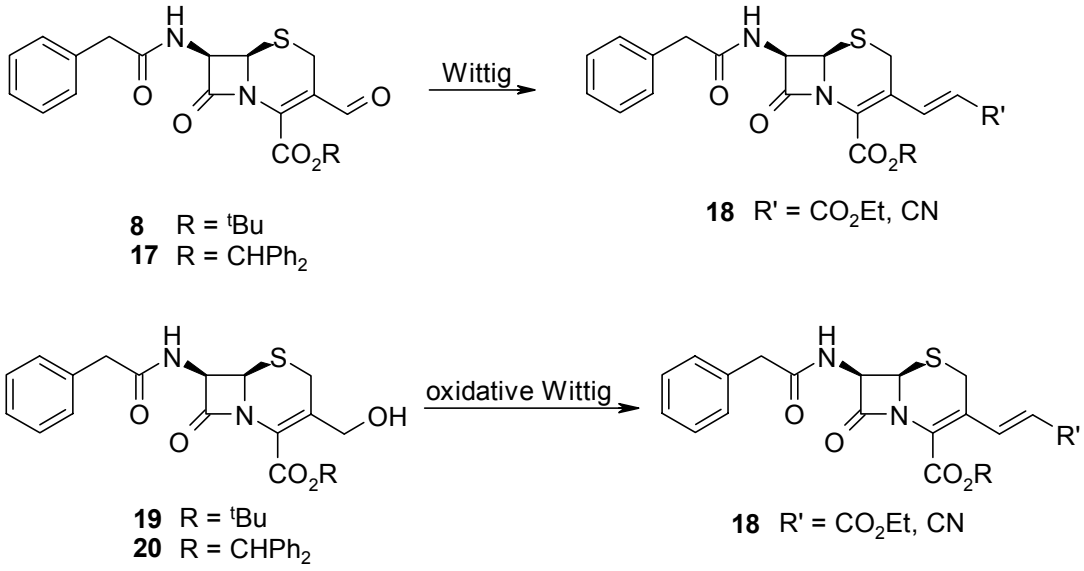
synthesis of 3-norcephalosporins **16** using the Barton radical decarboxylation reaction. A remarkable difference was encountered in the reactivity and stability of the Δ^2- and Δ^3-isomers. Several non-carbon substituents (chloride, bromide, iodide, and hydrogen) were introduced at C_3 in modest to good yields via Barton ester **15** (Scheme 4). The (halo)-decarboxylation reactions represent for the first time the use of radical chemistry in the synthesis of 3-norcephalosporins.



Scheme 4.

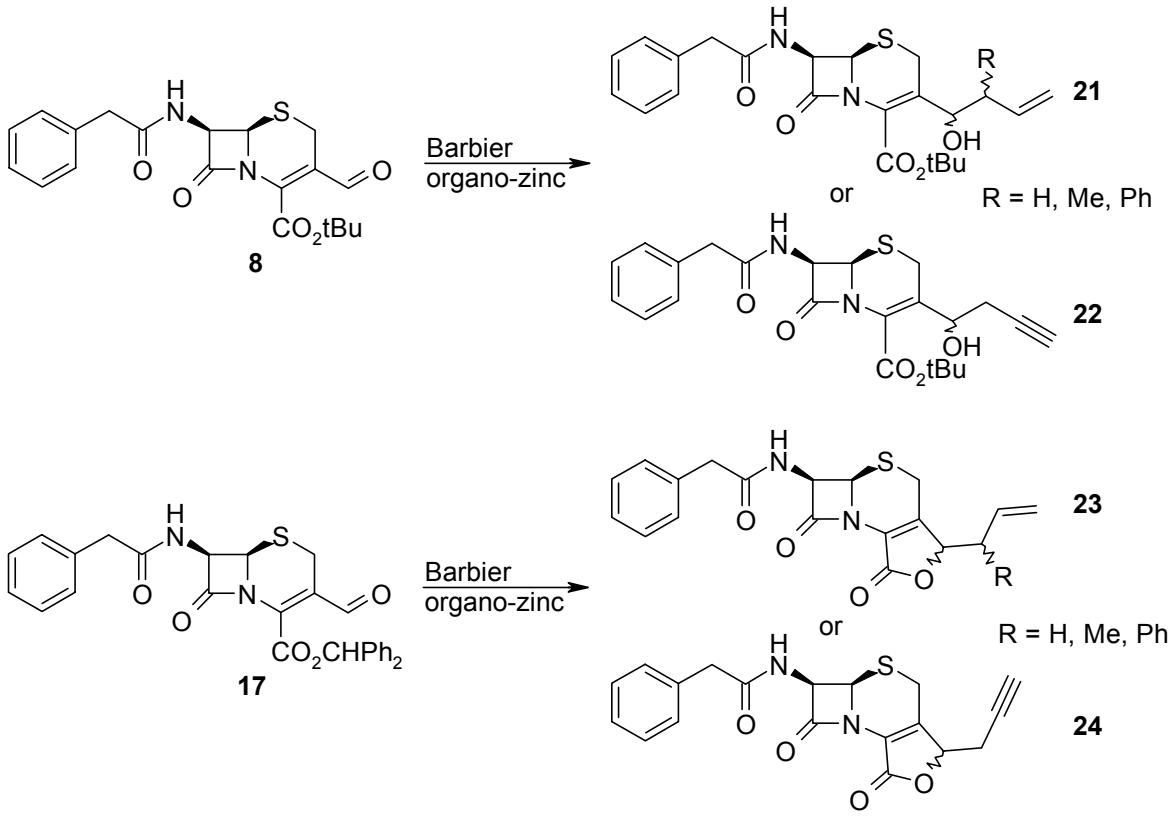
In **Chapter 6**, some Wittig olefination reactions of 3-formylcephalosporins **8** and **17** are described. Moderate yields of the corresponding alkenyl products **18** were obtained with phosphorous ylides stabilized by conjugation, *viz*. for ester and cyano substituted ylides. The direct olefination of 3-hydroxymethylcephalosporins **19** and **20**, employing an oxidative Wittig process, was accomplished with the same type of ylides, again in reasonable yields (Scheme 5).

Disappointingly, the olefination of 3-formylcephalosporins with non-stabilized ylides was not met with success, only decomposition of the cephalosporin nucleus was observed. Alternative routes to 3-alkenylcephalosporins also failed to give the desired products.



Scheme 5.

The allylation and propargylation of 3-formylcephalosporins **8** and **17** under zinc-mediated Barbier conditions are described in **Chapter** 7. The corresponding homoallylic and homopropargylic alcohols **21-24** were produced in good yields and with good to excellent diastereoselectivity (Scheme 6). Preliminary synthetic studies directed to cephalothin and cefprozil analogues conclude this chapter.

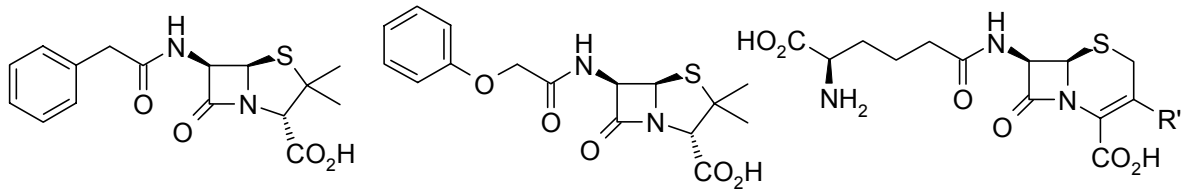


Scheme 6.

In summary, this thesis describes the synthesis and exploration of 3-formylcephalosporins. Novel chemistry of 3-formylcephalosporins is highlighted by their use in a new convenient synthesis of 3-carboxycephalosporins, key-intermediates for the preparation of 3-norcephalosporins, and their use in a highly diastereoselective zinc-mediated Barbier-type allylation and propargylation reaction. The Barton radical decarboxylation reaction was successfully used for the synthesis of various 3- and 4-norcephalosporins. A summary in English and Dutch concludes this thesis.

SAMENVATTING

De geschiedenis van de levensreddende β-lactam antibiotica begon in 1928 door de toevallige ontdekking van penicilline G (**1**) door Alexander Fleming (Figuur 1). Enkele belangrijke andere mijlpalen in deze geschiedenis zijn de voltooiing van de totaalsynthese van penicilline V (**2**) in 1957, de ontdekking van de cefalosporines, een nieuwe familie van antibiotica met een breed spectrum activiteit, geïnitieerd door de vondst van cefalosporine C (**3**). Deze nieuwe klasse van β-lactam antibiotica opende een geheel nieuw onderzoeksgebied, met als doel het zoeken naar en bestuderen van actievere antibacteriële verbindingen. Het gevolg hiervan was, dat talrijke nieuwe penicilline en cefalosporines werden ontwikkeld, waarvan vele met succes op de markt gebracht zijn.



1 penicilline G **2** penicilline V **3** cefalosporine C

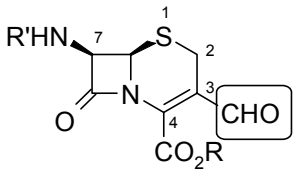
Figuur 1.

Ondanks deze successen is het aantal incidenten met betrekking tot de resistentie van bepaalde bacteriën voor antibiotica fors toegenomen. Daarom gaat tegenwoordig nog steeds veel aandacht uit naar de ontwikkeling van nieuwe cefalosporine antibiotica met verbeterde antibacteriële werking tegen resistente bacteriestammen. In deze context is de ontwikkeling van nieuwe synthesemethodieken en reacties buitengewoon belangrijk. Dit proefschrift handelt over de syntheses van nieuwe β-lactam antibiotica uit 3-formylcefalosporines als belangrijke intermediairen (Figuur 2). Het onderzoek is vooral toegespitst op de ontwikkeling van nieuwe synthesemethodieken en reacties om chemische omzettingen te bewerkstelligen in cefalosporine moleculen. Met in het achterhoofd dat 3-formylcefalosporines in de toekomst mogelijk beschikbaar komen uit fermentatieprocessen, past de ontwikkeling van nieuwe chemie rond deze 3-formyl derivaten uitstekend in het clusterproject "fijn chemie", dat zich tot doel stelt efficiënte schone (bio)katalytische routes voor β-lactam antibiotica te ontwikkelen.

In **Hoofdstuk 1** wordt relevante achtergrondinformatie gegeven over het onderzoek. Er wordt vooral aandacht besteed aan de ontstaansgeschiedenis van de β-lactam

antibiotica, het werkingsmechanisme van deze antibacteriële verbindingen en het probleem van de toenemende resistentie van bepaalde bacteriën voor β-lactam antibiotica.

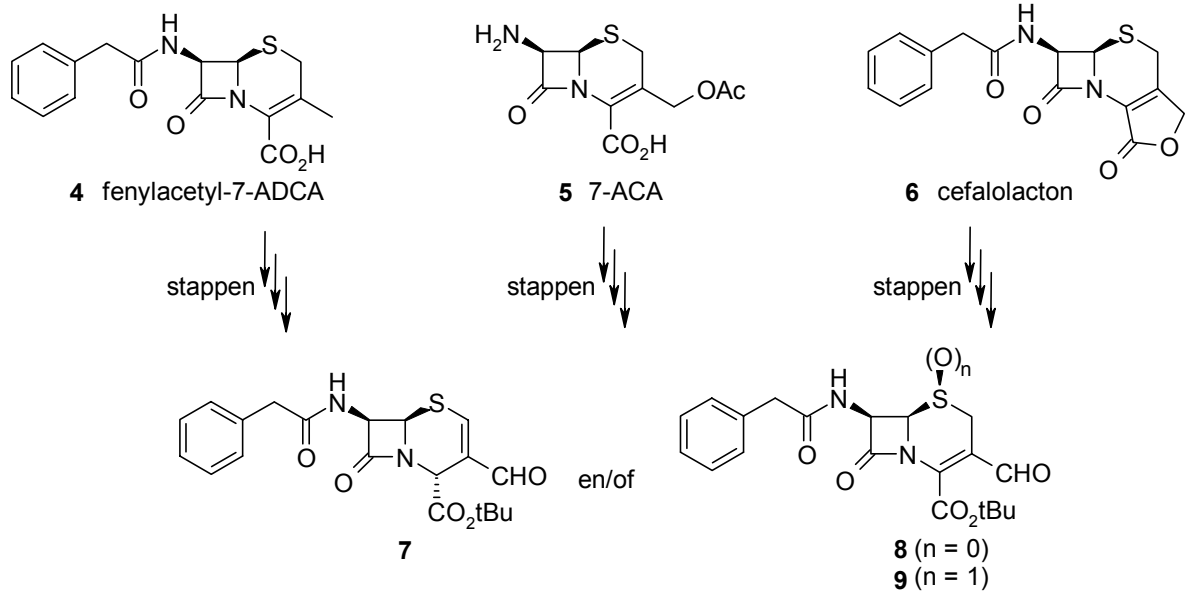
Een overzicht van relevante literatuur over 3-formylcephalosporines wordt behandeld in **Hoofdstuk 2**. In dit overzicht komen verschillende aspecten van de chemie van 3-formylcefalosporines, de belangrijke intermediairen in dit proefschrift, aan bod. Allereerst worden alle gerapporteerde syntheses van 3-formyl-cefalosporines in het kort samengevat. Het tweede deel handelt over de toepassingen en reacties van 3-formylcefalosporines. In dit kader wordt speciaal aandacht geschonken aan het chemische gedrag van de 3-formylgroep (Figuur 2).



3-formylcefalosporines

Figuur 2.

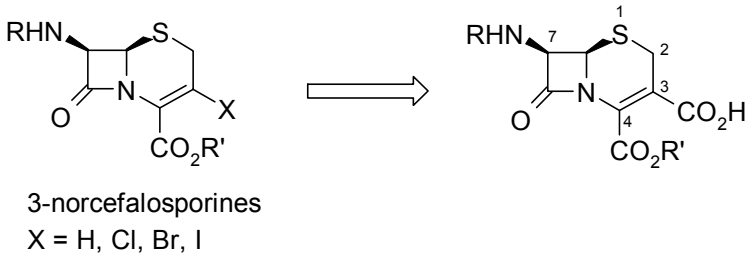
De ontwikkeling van een nieuwe algemeen toepasbare synthesemethodiek voor de bereiding van 3-formylcefalosporines uit goedkope en eenvoudig verkrijgbare grondstoffen wordt beschreven in **Hoofdstuk 3**.



Schema 1.

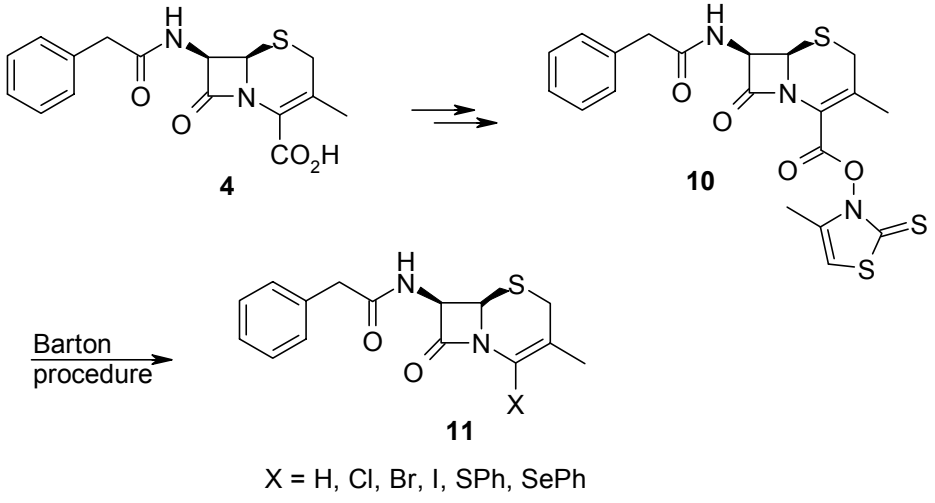
Uitgaande van fenylacetyl beschermd 7-aminodesacetylcefalosporaanzuur, (7-fenylacetyl-ADCA) **4**, 7-amino-cefalosporaanzuur (7-ACA) (**5**) en cefalolacton **6**, werden 3-formylcefalosporines **7-9** gesynthetiseerd in hoge opbrengsten (Schema 1). De keuze van de beschermgroepen, het chemische gedrag in relatie met de positie van de dubbele binding in de zesring, alsmede de oxidatietoestand van het zwavel atoom zijn hierin belangrijke aspecten. Hoewel 7-fenylacetyl-ADCA **4** en cefalolacton **6** bruikbaar zijn als uitgangsstoffen, is de efficiëntie van de routes voor 3-formylcefalosporines uitgaande van deze twee verbindingen inferieur aan de route die gebruikmaakt van 7-ACA (**5**).

In **Hoofdstuk 4** wordt een studie naar de synthese van 3-norcefalosporines beschreven (Schema 2).



Schema 2.

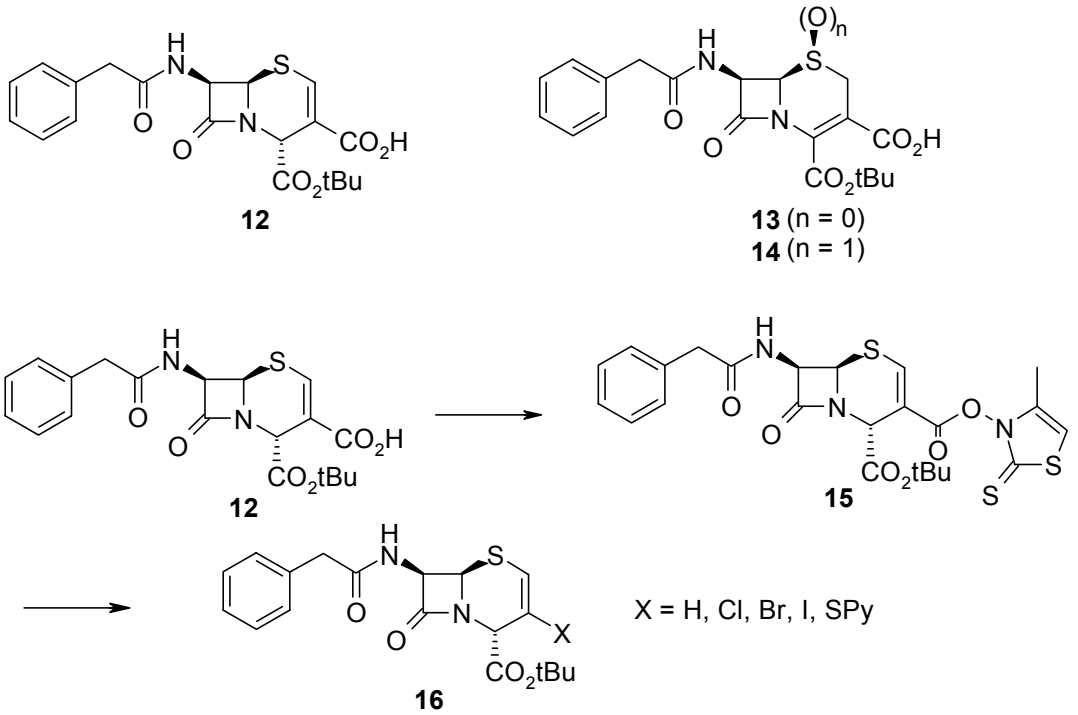
Er worden zowel ionogene als radicalaire benaderingen behandeld om een (halo)-decarboxylering in de modelverbinding 7-fenylacetyl-ADCA **4** te bewerkstelligen. Door gebruik te maken van de radicalaire decarboxylatie reactie van Barton, werd een verscheidenheid aan 4-gefunctionaliseerde cefalosporines **11** gesynthetiseerd via Barton ester **10** (Schema 3).



Schema 3.

In de omzettingsreactie van de carboxylfunctie in een waterstof-, chloor-, broom- of jood-substituent, alsmede voor de introductie van selenium- en zwavelbevattende groepen op de 4-positie werden matige tot goede opbrengsten verkregen.

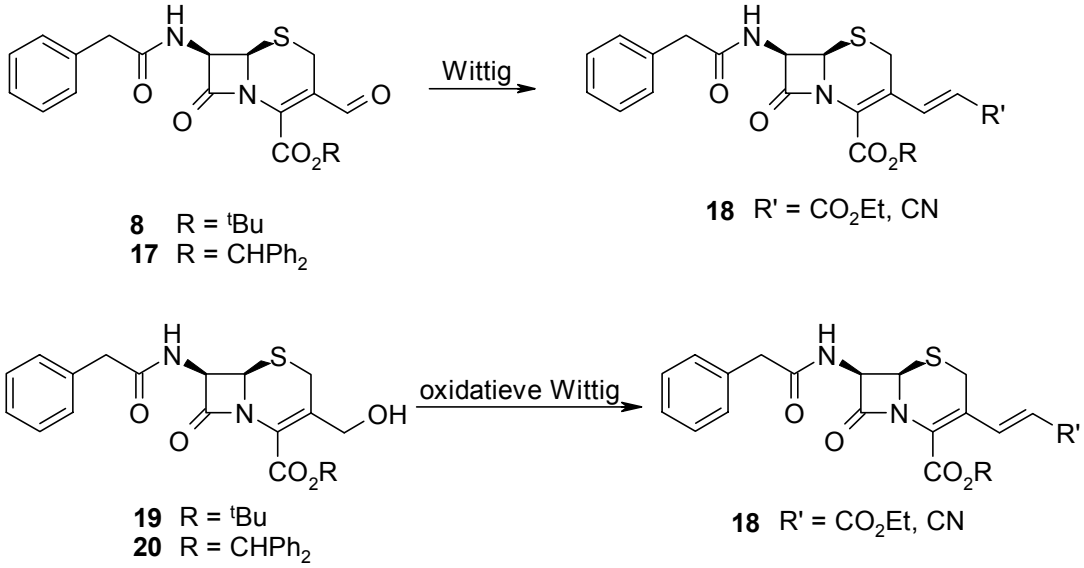
Een nieuwe verbeterde methode voor de bereiding van 3-carboxycefalosporines **12-14** uit 3-formylcefalosporines werd ontwikkeld (**Hoofdstuk 5**). Deze verbindingen kunnen gebruikt worden voor verder functionalisering op de C_3 positie. De 3-carboxycefalosporines **12-14** kunnen worden gebruikt als belangrijke intermediairen voor de ontwikkeling van een nieuwe syntheseroute voor 3-norcefalosporines **16**, door gebruik te maken van de Barton radicalaire decarboxyleringsreactie. In deze reactie was een opvallend verschil waar te nemen in de reactiviteit en stabiliteit tussen de Δ^2- en Δ^3-isomeren. Verschillende niet-koolstofsubstituenten (chloor, broom, jood en waterstof) werden geïntroduceerd op de C_3-positie in matige tot goede opbrengsten via Barton ester **15** (Schema 4). De (halo)-decarboxyleringsreacties laten voor het eerst het gebruik zien van radicaalchemie voor de synthese van 3-norcefalosporines.



Schema 4.

In **Hoofdstuk 6** worden enkele Wittig olefineringsreacties van 3-formylcefalosporines **8** en **17** beschreven. Met door conjugatie gestabiliseerde fosforylides werden in redelijke opbrengsten de overeenkomstige alkenylproducten **18** verkregen. Door een oxidatieve Wittig procedure toe te passen, gebruikmakend

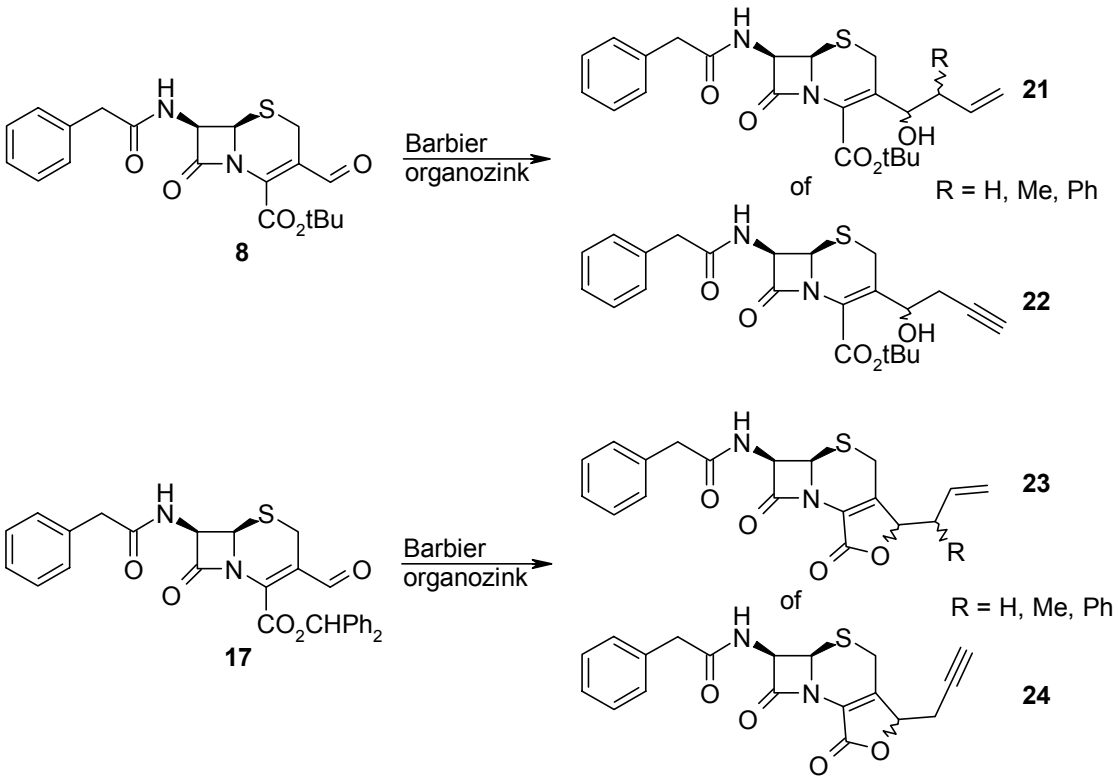
van hetzelfde type ylides, konden 3-hydroxymethylcefalosporines **19** en **20** direct worden omgezet in de overeenkomstige alkenyl producten **18** in redelijke opbrengsten (Schema 5).



Schema 5.

De olefinering van 3-formylcefalosporines met niet-gestabiliseerde ylides was helaas geen succes. Er werd slechts ontleding van de cefalosporine-kern waargenomen. Alternatieve routes naar 3-alkenylcefalosporines leverden ook niet de gewenste resultaten op.

De reacties van 3-formylcefalosporines **8** en **17** met (gesubstitueerde) allylbromides en propargylbromide onder Barbier condities worden beschreven in **Hoofdstuk 7**. De overeenkomstige homoallyl- en homopropargyl-alcoholen **21-24** werden gevormd in goede opbrengsten en met een goede tot excellente diastereoselectiviteit (Schema 6). Een eerste aanzet voor de synthese van cefalothin en cefprozil analoga besluit dit hoofdstuk.



Schema 6.

Samenvattend kan worden gesteld, dat het onderzoek beschreven in dit proefschrift nieuwe chemie omtrent 3-formylcefalosporines heeft opgeleverd. Deze nieuwe chemie komt naar voren bij het gebruik van 3-formylcefalosporines in een nieuwe efficiënte synthese van 3-carboxycefalosporines, belangrijke intermediairen in de bereiding van 3-norcefalosporines, en bij het gebruik van 3-formylcefalosporines in de diastereoselectieve Barbiertype organozink allylerings- en propargyleringsreactie. De Barton radicalaire decarboxyleringsreactie werd met succes toegepast in de synthese van verschillende 3- en 4-norcefalosporines.

Samenvattingen in het Engels en Nederlands besluiten dit proefschrift.

LIST OF PUBLICATIONS AND PRESENTATIONS

Thuring, J.W.J.F.; Keltjens, R.; Nefkens, G.H.L.; Zwanenburg, B. Synthesis and Biological Evaluation of Potential Substrates for the Isolation of the Strigol Receptor, *J. Chem. Soc. Perkin Trans. 1*, **1997**, 759.

Keltjens, R.; Vadivel, S.K.; De Vroom, E.; Klunder, A.J.H.; Zwanenburg, B. A New Convenient Synthesis of 3-Carboxycephalosporins Starting from 7-Aminocephalosporanic Acid (7-ACA), *Eur. J. Org. Chem.* **2001**, 2529.

Keltjens, R.; Vadivel, S.K.; Klunder, A.J.H.; Zwanenburg, B. Synthesis of 3-Nor-cephalosporins *via* Barton's Radical Decarboxylation Reaction, *in preparation*.

Keltjens, R.; Vadivel, S.K.; Klunder, A.J.H.; Zwanenburg, B. Diastereoselective Barbier Type Organozinc Additions to 3-Formylcephalosporins, *in preparation*.

Keltjens, R.; Thuring, J.W.J.F.; Nefkens, G.H.L.; Zwanenburg, B. *Synthesis and Biological Evaluation of Potential Substrates for the Isolation of the Strigol Receptor*, oral communication during 5th Bologna-Nijmegen mini-symposium "Bonymi-V", University of Camerino (Italy), September 10-17, 1996.

Keltjens, R.; Vadivel, S.K.; Klunder, A.J.H.; Zwanenburg, B. *The Development of a New Synthesis of 7-ACCA (Cefaclor)*, oral communication during the annual meeting of the Cluster Project "Fine-Chemistry", Vaalsbroek (The Netherlands), October 28-30, 1998.

Keltjens, R.; Vadivel, S.K.; Klunder, A.J.H.; Zwanenburg, B. *Synthesis and Chemistry of 3-Formylcephalosporins*, oral communication during the annual meeting of the Cluster Project "Fine-Chemistry", Vaalsbroek (The Netherlands), March 29-31, 2000.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 9 april 1972 te Horst. In juni 1990 behaalde hij het vwo-diploma aan scholengemeenschap "St. Thomascollege" te Venlo. In datzelfde jaar begon hij aan de Katholieke Universiteit Nijmegen met de studie scheikunde, waarvoor hij in 1991 het propedeutisch examen haalde. In augustus 1996 slaagde hij voor het doctoraal examen scheikunde met als uitgebreide hoofdrichting Organische Chemie (Prof. dr. B. Zwanenburg) en als nevenrichting Chemische Microbiologie (Prof. dr. G.D. Vogels). Daarnaast werd een extra nevenrichting Industriële Chemie (Prof. dr. A. Bruggink) en bijbehorende stage bij DSM Research te Geleen doorlopen.

Van oktober 1996 tot november 2000 was hij als Assistent in Opleiding (AIO) verbonden aan het NSR Center for Molecular Structure, Design, and Synthesis bij de vakgroep Organische Chemie. Onder leiding van Prof. dr. B. Zwanenburg en Dr. A.J.H. Klunder en in samenwerking met Dr. E. de Vroom (DSM Anti-Infectives) verrichte hij het in dit proefschrift beschreven onderzoek. Het onderzoek werd uitgevoerd in het kader van het Clusterproject "Fijn-Chemie", een samenwerkingsproject tussen DSM Research (Geleen), DSM Anti-Infectives (Delft) en vijf universitaire groepen.

Tijdens de studie en het promotieonderzoek werd gedurende twee jaargangen een bijdrage geleverd aan de eerste fase onderwijs aan scheikundestudenten in de vorm van practica. Tijdens het studiejaar 1999/2000 verzorgde hij het Tutor-uur voor studenten van de afdeling Organische Chemie.

Sinds 1 december 2000 is de auteur werkzaam bij Synthon BV in Nijmegen.